Ray PEAT

1936–2022

The Collected Works

Perceive. Think. Act.

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Perceive. Think. Act.

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Perceive. Think. Act.

When people start thinking about the things in their life that can be changed, they are exercising aspects of their organism that had been atrophied by being in an authoritarian culture. Authoritarians talk about protocols, but the only valid "protocol" would be something like "perceive, think, act."

— Ray Peat

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Academic Authoritarians, Language, Metaphor, Animals, and Science

Ray Peat's Newsletter, 2009

A few years ago a group of researchers in Scotland studying learning in apes did some experiments (involving opening boxes to get a piece of candy inside) that showed that chimpanzees learn in a variety of "flexibly adaptive" ways, and that 3 year old children being presented with a similar task most often did it in ways that appear to be less intelligent than the apes. They "suggest that the difference in performance of chimpanzees and children may be due to a greater susceptibility of children to cultural conventions."[1,2]

In my newsletter on puberty, I described some of the effects of foods and hormones on intelligence. Here, I want to consider the effects of culture on the way people learn and think. Culture, it seems, starts to make us stupid long before the metabolic problems appear.

For many years I described culture as the perceived limits of possibility, but people usually prefer to think of it as the learned rules of conduct in a society. In the late 1950s I was talking with a psychologist about the nature of "mental maps," and I said that I found my way around campus by reference to mental pictures of the locations of things, and he said that his method was to follow a series of rules, "go out the front door and turn left, turn left at the first corner, walk three blocks and turn right, …up the stairs, turn right, fourth office on the left." He had been studying mental processes for about 40 years, so his claim made an impression on me.

I thought this style of thinking might have something to do with the growing technological preference for digital, rather than analog, devices. The complexity and continuity of the real world is made to seem more precise and concrete by turning it into rules and numbers.

Around the same time, I found that some people dream in vivid images, while others describe dreams as "listening to someone tell a story."

Several years later, a graduate student of "language philosophy" from MIT told me that I was just confused if I believed that I had mental images that I could use in thinking. His attitude was that language, in its forms and in the ways it could convey meaning, was governed by rules.

He was part of an effort to define consciousness in terms of rules that could be manipulated formally. This was just a new variation on the doctrine of an "ideal language" that has concerned many philosophers since Leibniz, but now its main use is to convince people that cultural conventions and authority are rooted in the nature of our minds, rather than in particular things that people experience and the ways in which they are treated.

George Orwell, whose novels showed some of the ways language is used to control people, believed that language should be like a clear window between minds, but knew that it was habitually used to distort, mislead, and control. Scientific and medical practices often follow the authority of culture and indoctrination, instead of intelligently confronting the meaning of the evidence, the way chimpanzees are able to do.

Not so many years ago, people believed that traits were "determined by genes," and that the development of an organism was the result of—was caused by—the sequential expression of genes in the nucleus of the fertilized egg. When B.F. Skinner in the 1970s said "a gestating baby isn't influenced by what happens to its mother," he was expressing a deeply rooted bio-medical dogma. Physicians insisted that a baby couldn't be harmed by its mother's malnutrition, as long as she lived to give birth. People could be quite vicious when their dogma was challenged, but their actions were systematically vicious when they weren't challenged.

An ovum doesn't just grow from an oocyte according to instructions in its genes, it is constructed, with surrounding nurse cells adding substances to its cytoplasm. Analogously, the fertilized egg doesn't just grow into a human being, it is constructed, by interactions with the mother's physiology. At birth, the environment continues to influence the ways in which cells develop and interact with each other.

Even during adulthood, the ways in which our cells—in the brain, immune system, and other organs—develop and interact are shaped by the environment. When Skinner was writing, many biologists still believed that each synapse of a nerve was directed by a gene, and couldn't be influenced by experience.

Our brain grows into our culture, and the culture lives in our nervous system. If a person grows up without hearing people speak, he will have grown a special kind of brain, making it difficult to learn to speak. (Genie, wolf boy, Kaspar Hauser, for example.)

When we ask a question and find an answer, we are changed. Thinking with learning is a developmental process. But many people learn at an early age not to question. This changes the nature of subsequent learning and brain development.

In the 1960s, many textbooks were published that claimed to use scientific language theory to improve the instruction of English, from grade school level to college level. They didn't work, and at the time they were being published they appeared fraudulent to people who didn't subscribe to the incipient cults of "Generative Grammar" and "Artificial Intelligence" that later developed into "Cognitive Science."

At the time that Artificial Intelligence was coming to the attention of investors and academicians, Neodarwinism had already cleansed the university biology departments of its opponents who advocated more holistic views, and the idea of a brain that was "hard-wired" according to genetic instructions had entered both neurology and psychology. The field concept was disappearing from developmental biology, as Gestalt psychology was disappearing from the universities and journals.

In the humanities and social sciences, a fad appeared in the 1960s, in which a theory of grammar advocated by Noam Chomsky of MIT was said to explain human thinking and behavior, and specialists in anthropology, psychology, literature, rhetoric, sociology, and other academic fields, claimed that it informed their work in an essential way. The rapid spread of a doctrine for which there was essentially no evidence suggests that it was filling a need for many people in our culture. This doctrine was filling some of the gaps left by the failure of genetic determinism that was starting to be recognized. It gave new support to the doctrine of inborn capacities and limitations, in which formulaic indoctrination can be justified by the brain's natural structure.

Chomsky was committed to an idealistic, "rationalist" doctrine of innate ideas, and to argue for that doctrine, which held that there are transcendent forms (or "deep structures") that control mind, he disposed of the opposing "empiricist" approach to mind by claiming that children simply learn language so rapidly that it would be impossible to explain on the basis of learning from experience. Separating vocabulary from grammar, he acknowledged that each language is different, and can be learned as easily by the children of immigrants of different ethnicity as by children whose ancestors spoke it, but that all humans have a genetically encoded "universal grammar," a "language organ." It is this

"inborn grammar" that allows children to learn what he said would be inconceivable to learn so quickly from experience.

The abstract, computational nature of the "inborn" functions of the "language organ" would make a nice program for a translating machine, and the absence of such a useful program, after more than 50 years of trying to devise one, argues against the possibility of such a thing.

Since Plato's time, some people have believed that, behind the changing irregularities of real languages, there is a timeless, context-free language. In the late 1950s, when I was studying language and the "ideal languages" of the philosophers, I realized that George Santayana was right when he pointed out that each time an artificial language is used by real people in real situations, it is altered by the experience that accrues to each component, from the context in which it is used. If real language were the model for mathematics, then the values of numbers would change a little with every calculation.

Adults are usually slower than children at learning a new language, but they can make the process much quicker by memorizing paradigms. With those models, they can begin speaking intelligible sentences when they know only a few words. These basics of grammar are often outlined in just a few pages, but listing irregularities and exceptions can become very detailed and complex. The grammar that children use isn't as subtle as the grammar some adults use, and college freshmen are seldom masters of the grammar of their native language.

There have been various studies that have investigated the number of words understood by children at different ages.

The Virginia Polytechnic Institute website says that:

- By age 4 a person probably knows 5,600 words
- By age 5 a person probably knows 9,600 words
- By age 6 a person probably knows 14,700 words
- By age 7 a person probably knows 21,200 words
- By age 8 a person probably knows 26,300 words
- By age 9 a person probably knows 29,300 words
- By age 10 a person probably knows 34,300 words
- By age 20 a college sophomore probably knows 120,000 words

A dictionary with 14,000 words is a substantial book. The grammar used by a 6 year old person isn't very complex, because at that age a

person isn't likely to know all of the subtleties of their language. There is no reason to assume that a mind that can learn thousands of words and concepts in a year can't learn the grammatical patterns of a language—a much smaller number of patterns and relationships—in a few years.

Idioms and clichés are clusters of words that are frequently used together in the same pattern to express a stereotyped meaning. There are thousands of them in English, and some of them have existed for centuries, while others are regional and generational. It is possible to speak or write almost completely in clichés, and they are such an important part of language that their acquisition along with the basic vocabulary deserves more attention than linguists have given it. A mind that can learn so many clichés can certainly learn the relatively few stereotypical rules of phrasing that make up the grammar of a language. In fact, a grammar in some ways resembles a complex cliché.

Recognition of patterns, first of things that are present, then of meaningful sequences, is what we call awareness or consciousness. There is biological evidence, from the level of single cells through many types of organism, both plant and animal, that pattern recognition is a basic biological function. An organism that isn't oriented in space and time isn't an adapted, adapting, organism. Environments change, and the organization of life necessarily has some flexibility.

A traveling bird or dog can see a pattern once, and later, going in the opposite direction, can recognize and find specific places and objects. An ant or bee can see a pattern once, and communicate it to others.

If dogs and birds lived in colonies or cities, as bees and ants do, and carried food home from remote locations, they might have a need to communicate their knowledge. The fact that birds and dogs use their vocal organs and brains to communicate in ways that people have seldom cared to study doesn't imply that their brains differ radically from human brains in lacking a "language organ."

People whose ideology says that "animals use instinct rather than intelligence," and that they lack "the language instinct," refuse to perceive animals that are demonstrating their ability to generalize or to understand language.

Organisms have genes, so a person could say that pattern recognition is genetically determined, but it would be a foolish and empty thing to say. (Nevertheless, people do say it.) The people who believe that there are "genes for grammar" believe that these mind-controlling genes give

us the ability to generalize, and therefore say that animals aren't able to generalize, though their "instinctive behaviors" might sometimes seem to involve generalization.

In language, patterns are represented symbolically by patterned sounds, and some of those symbolically represented patterns are made up of other patterns. Different languages have different ways of representing different kinds of patterns.

"Things" are recognizable when they are far or near, moving or still, bright or dark, or upside down, because the recognition of a pattern is an integration involving both spatial and temporal components. The recognition of an object involves both generalization and concreteness.

Things that are very complex are likely to take longer to recognize, but the nature of any pattern is that it is a complex of parts and properties.

A name for "a thing" is a name for a pattern, a set of relationships.

The method of naming or identifying a relationship can make use of any way of patterning sound that can be recognized as making distinctions. Concepts and grammar aren't separable things, "semantics" and "syntax" are just aspects of a particular language's way of handling meaning.

As a child interacts with more and more things, and learns things about them, the patterns of familiar things are compared to the patterns of new things, and differences and similarities are noticed and used to understand relationships. The comparison of patterns is a process of making analogies, or metaphors. Similarities perceived become generalizations, and distinctions allow things to be grouped into categories.

When things are explored analogically, the exploration may first identify objects, and then explore the factors that make up the larger pattern that was first identified, in a kind of analysis, but this analysis is a sort of expansion inward, in which the discovered complexity has the extra meaning of the larger context in which it is found.

When something new is noticed, it excites the brain, and causes attention to be focused, in the "orienting reflex." The various senses participate in examining the thing, in a physiological way of asking a question. Perception of new patterns and the formation of generalizations expands the ways in which questions are asked. When words are available, questions may be verbalized. The way in which questions are answered verbally may be useful, but it often diverts the questioning process, and provides rules and arbitrary generalizations that may take

the place of the normal analogical processes of intelligence. The vocabulary of patterns no longer expands spontaneously, but tends to come to rest in a system of accepted opinions.

A few patterns, formulated in language, are substituted for the processes of exploration through metaphorical thinking. In the first stages of learning, the process is expansive and metaphorical. If a question is closed by an answer in the form of a rule that must be followed, subsequent learning can only be analytical and deductive.

Learning of this sort is always a system of closed compartments, though one system might occasionally be exchanged for another, in a "conversion experience."

The exploratory analogical mind is able to form broad generalizations and to make deductions from those, but the validity of the generalization is always in a process of being tested. Both the deduction and the generalization are constantly open to revision in accordance with the available evidence.

If there were infallible authorities who set down general rules, language and knowledge could be idealized and made mathematically precise. In their absence, intelligence is necessary, but the authorities who would be infallible devise ways to confine and control intelligence, so that, with the mastery of a language, the growth of intelligence usually stops.

In the 1940s and '50s, W.J.J. Gordon organized a group called Synectics, to investigate the creative process, and to devise ways to teach people to solve problems effectively. It involved several methods for helping people to think analogically and metaphorically, and to avoid stereotyped interpretations. It was a way of teaching people to recover the style of thinking of young children, or of chimps, or other intelligent animals.

When the acquisition of language is burdened by the acceptance of clichés, producing the conventionalism mentioned by Horner and Whiten, with the substitution of deductive reasoning for metaphorical-analogical thinking, the natural pleasures of mental exploration and creation are lost, and a new kind of personality and character has come into existence.

Bob Altemeyer spent his career studying the authoritarian personality, and has identified its defining traits as conventionalism, submission to authority, and aggression, as sanctioned by the authorities. His last book, *The Authoritarians* (2006) is available on the internet.

Altemeyer found that people who scored high on his scale of authoritarianism tended to have faulty reasoning, with compartmentalized thinking, making it possible to hold contradictory beliefs, and to be dogmatic, hypocritical, and hostile.

Since he is looking at a spectrum, focusing on differences, I think he is likely to have underestimated the degree to which these traits exist in the mainstream, and in groups such as scientists, that have a professional commitment to clear reasoning and objectivity. With careful training, and in a culture that doesn't value creative metaphorical thinking, authoritarianism might be a preferred trait.

Konrad Lorenz (who with Niko Tinbergen got the Nobel Prize in 1973) believed that specific innate structures explained animal communication, and that natural selection had created those structures. Chomsky, who said that our genes create an innate "Language Acquisition Device," distanced himself slightly from Lorenz's view by saying that it wasn't certain that natural selection was responsible for it. However, despite slightly different names for the hypothetical innate "devices," their views were extremely similar.

Both Lorenz and Chomsky, and their doctrine of innate rule-based consciousness, have been popular and influential among university professors. When Lorenz wrote a book on degeneration, which was little more than a revised version of the articles he had written for the Nazi party's Office for Race Policy in the late 1930s and early 1940s, advocating the extermination of racial "mongrels" such as jews and gypsies, most biologists in the U.S. praised it. Lorenz identified National Socialism with evolution as an agent of racial purification. His lifelong beliefs and activities—the loyalty to a strong leader, advocating the killing of the weak—identified Lorenz as an extreme authoritarian.

When a famous professor went on a lecture tour popularizing and affirming the scientific truth and importance of those publications, and asserting that all human actions and knowledge, language, work, art, and belief, are specified and determined by genes, he and his audience (which, at the University of Oregon, included members of the National Academy of Sciences and Jewish professors who had been refugees from Nazism, who listened approvingly) were outraged when a student mentioned the Nazi origin and intention of the original publications.

They said "you can't say that a man's work has anything to do with his life and political beliefs," but in fact the lecturer had just finished

saying that everything a person does is integral to that person's deepest nature, just as Lorenz said that a goose with a pot belly and odd beak, or a person with non-nordic physical features and behavior and cultural preferences—should be eliminated for the improvement of the species. Not a single professor in the audience questioned the science that had justified Hitler's racial policies, and some of them showed great hostility toward the critic.

In the 1960s, a professor compared graduate students' scores on the Miller Analogies Test, which is a widely used test of analogical thinking ability, to their academic grades. She found that the students who scored close to the average on the test had the highest grades and the greatest academic success, and those who deviated the most from the average on that test, in either direction, had the worst academic grades. If the ability to think analogically is inversely associated with authoritarianism, then her results would indicate that graduate schools select for authoritarianism. (If not, then they simply select for mediocrity.)

Although Bob Altemeyer's scale mainly identified right-wing, conservative authoritarians, he indicated that there could be left-wing authoritarians, too. Noam Chomsky is identified with left-wing political views, but his views of genetic determinism and a "nativist" view of language learning, and his anti-empiricist identification of himself as a philosophical Rationalist, have a great correspondence to the authoritarian character. The "nativist" rule-based nature of "Cognitive Science" is just the modern form of an authoritarian tradition that has been influential since Plato's time.

The first thing a person is likely to notice when looking at Chomsky's work in linguistics is that he offers no evidence to support his extreme assertions. In fact, the main role evidence plays in his basic scheme is negative, that is, his doctrine of "Poverty of the Stimulus" asserts that children aren't exposed to enough examples of language for them to be able to learn grammar—therefore, grammar must be inborn.

I think Chomsky discovered long ago that the people around him were sufficiently authoritarian to accept assertions without evidence if they were presented in a form that looked complexly technical. Several people have published their correspondence with him, showing him to be authoritarian and arrogant, even rude and insulting, if the person questioned his handling of evidence, or the lack of evidence.

For example, people have argued with him about the JFK assassination, U.S. policy in the Vietnam war, the HIV-AIDS issue, and the 9/11 investigation. In each case, he accepts the official position of the government, and insults those who question, for example, the adequacy of the Warren Commission report, or who believe that the pharmaceutical industry would manipulate the evidence regarding AIDS, or who doubt the conclusions of the 9/11 Commission investigation.

He says that investigation of such issues is "diverting people from serious issues," as if those aren't serious issues. And "even if it's true" that the government was involved in the 9/11 terrorism, "who cares? I mean, it doesn't have any significance. I mean it's a little bit like the huge amount of energy that's put out on trying to figure out who killed John F. Kennedy. I mean, who knows, and who cares… plenty of people get killed all the time. Why does it matter that one of them happens to be John F. Kennedy?"

"If there was some reason to believe that there was a high level conspiracy" in the JFK assassination, "it might be interesting, but the evidence against that is just overwhelming." "And after that it's just a matter of, uh, if it's a jealous husband or the mafia or someone else, what difference does it make?" "It's just taking energy away from serious issues onto ones that don't matter. And I think the same is true here," regarding the events of 9/11. These reactions seem especially significant, considering his reputation as America's leading dissenter.

The speed with which Chomskyism spread through universities in the U.S. in the 1960s convinced me that I was right in viewing the instruction of the humanities and social sciences as indoctrination, rather than objective treatment of knowledge. The reception of the authoritarian ideas of Lorenz and his apologists in biology departments offered me a new perspective on the motivations involved in the uniformity of the orthodox views of biology and medicine.

In being introduced into a profession, any lingering tendency toward analogical-metaphoric thinking is suppressed. I have known perceptive, imaginative people who, after a year or two in medical school, had become rigid rule-followers.

One of the perennial questions people have asked when they learn of the suppression of a therapy, is "if the doctors are doing it to defend the profitable old methods, how can they refuse to use the better method

even for themselves and their own family?" The answer seems to be that their minds have been radically affected by their vocational training.

For many years, cancer and inflammation have been known to be closely associated, even to be aspects of a single process. This was obvious to "analog minded" people, but seemed utterly improbable to the essentialist mentality, because of the indoctrination that inflammation is a good thing, that couldn't coexist with a bad thing like cancer.

The philosophy of language might seem remote from politics and practical problems, but Kings and advertisers have understood that words and ideas are powerfully influential in maintaining relationships of power.

Theories of mind and language that justify arbitrary power, power that can't justify itself in terms of evidence, are more dangerous than merely mistaken scientific theories, because any theory that bases its arguments on evidence is capable of being disproved.

In the middle ages, the Divine Right of Kings was derived from certain kinds of theological reasoning. It has been replaced by newer ideologies, based on deductions from beliefs about the nature of mind and matter, words and genes, "Computational Grammar," or numbers and quantized energy, but behind the ideology is the reality of the authoritarian personality.

I think if we understand more about the nature of language and its acquisition we will have a clearer picture of what is happening in our cultures, especially in the culture of science.

Adaptive Substances, Creative Regeneration

Mainstream Science, Repression, and Creativity

Ray Peat's Newsletter, 2008

More than 50 years have been wasted in one of the most important and fundamental branches of science and medicine, for reasons that are highly ideological and political. Rather than studying the regeneration of organs and tissues, and recognizing its obvious importance in healing as well as in understanding the nature of life, much of the last century was devoted to the defamation of the researchers who were making real progress in the field. Despite many demonstrations that regeneration can occur in adult mammals, students were taught that it happens only in lower vertebrates. I think it's important to look closely at the ideology responsible for this great loss.

Warburg and Szent-Györgyi, in thinking about cancer, emphasized that growth is the primordial function of all cells, and that the differentiated functions of complex organisms involve restraints of that primitive function, imposed by a system that has developed through time.

Seen with this orientation, regeneration is the spontaneous result of the disappearance of restraint. The reproduction of a whole plant from a twig, or clone, was a process known for thousands of years. Any part of the plant contains the information needed for making a whole plant. More than thirty years ago, cells from a tumor were added to the cells of a normal embryo, and the animal that matured from the embryo-tumor mix was normal, and had traits of both lineages, showing that the tumor cells had retained the genetic information of a complete healthy organism, and just needed a different environment in which to realize their full potential.

> "I intend to show you how neo-Darwinism has been invalidated within science itself, as an explanation of how life on earth has evolved and is evolving. It is nevertheless still perpetrated by the academic establishment, if only because it serves so well to promote genetic engineering, a technology that has the potential to destroy all life on earth. Furthermore, neo-Darwinism reinforces a worldview that undermines all moral values and prevents us from the necessary shift to holistic, ecological sciences that can truly regenerate the earth and revitalize the human spirit."
>
> — Mae-Wan Ho

One of the currents of medical thinking, from classical times through Paracelsus to homeopathy and naturopathy, has been a confidence in the capacity of the organism to heal itself. But "modern" medicine has arrogated to itself the "healing power," with terrible results, mitigated only by their occasional reluctant acceptance of fragments of sane organismic thinking, such as recognizing the importance of nutrition, or of keeping sewage out of the drinking water. Research into methods to support the organism's natural restorative powers has been ridiculed and suppressed.

We are immersed in the propaganda of modern medicine, and part of that propaganda involves the confabulation of a history of science that supports their practice and their ideology. The real history of science won't be found in science textbooks.

Mainstream medical treatments are based on some fundamentally absurd scientific ideas. The advent of experimental animal cloning and the industrialization of genetic engineering have undercut the most important biological doctrines of the 20th century, but the processes of critical thinking haven't made headway against most of the traditional medical stereotypes. Cloning shows that all cells are potential "stem cells," but this fact co-exists with the Hayflick doctrine, that says, essentially, that no cell is a stem cell.

The ideology of culturally significant "intellectuals"—scientists, professors, neurobiologists, linguists, philosophers, oncologists, geneticists—in the U.S. is deeply influenced by the dualism and mechanistic materialism of Rene DesCartes.

The denial that animals can think or understand language, the claim that babies or animals don't feel pain, or that heart cells and brain cells can't divide, or that somatic cells lack the genetic capacity to be cloned, or that they are intrinsically mortal, limited to a maximum of 50 cell divisions—these absurdities of 20th century biology and medicine all resulted from an abject commitment to the mechanistic doctrine of matter and life promoted or invented by DesCartes.

I doubt that DesCartes really invented anything, because, by the evidence of his writing, he wasn't an intelligent man, but he placed himself politically in such a way that his arguments were acceptable to many influential people, and they continue to be acceptable to authoritarian and elitist factions even today.

In the 16th and 17th century the cultures of England, Holland, and France were increasingly dominated by business interests. People who had money to invest wanted to see the world as an orderly, predictable place, and they found that many of the ideas of the ancient Greeks were useful. Mathematics was needed to calculate interest rates, insurance premiums, and, for the military, the trajectories of missiles. In an orderly world, allowance for a little random variation helped to save the perfection of the general rule.

In this environment, theological thinking began retrenching its doctrine, to make it more acceptable to the increasingly powerful commercial people. The clockwork universe of DesCartes' time, in which a perfect world that operated according to perfect natural laws had been divinely created, gradually became theologically acceptable during the 18th and 19th centuries. In the 18th century, the Deists were the most famous embodiment of the idea, and then in the 19th century their place was taken by the Catastrophists, who claimed that the fossils which seemed to show evolutionary change of species actually represented species that had been created along with those now existing, but that had been destroyed by catastrophes, such as Noah's flood. By the end of the 19th century, the president of an American university recognized that theological compromises could prevent his undergraduates from rejecting religion entirely, and forbade sermons against evolution.

There were many biologists who insisted that evolution of new species was analogous to the development of an individual, and that both revealed an adaptive capacity of the living substance. In this view, the adaptive growth of an individual in a new environment revealed novel solutions to new problems, and showed an innate inventiveness and intelligence in the process of growth and adaptation. The appearance of new species was thought to represent the same sorts of adaptive processes.

Erasmus Darwin (grandfather of Charles) was an evolutionist of this sort, but because of political and theological pressure, he kept relatively quiet about his beliefs. There was an underground culture, in which an evolutionary view of the world was accepted, but these views were seldom published, because of increasingly stringent censorship. Because of censorship, poetry, letters, and diaries, rather than academic and scholarly works, give us the true picture of 18th century and early 19th century scientific culture.

The scientists who wanted their work to be acceptable to those in power found ways to work with the Cartesian mechanical view of the world, building on the Deists' compromise, which had succeeded in removing the supernatural from nature. As the fossil evidence of evolution became inescapable, around the time of Charles Darwin's work, those who wanted to bring evolution into the mainstream of culture found that the Catastrophism of the creationists could be adapted to their purposes, with only slight modification.

The doctrine of Thomas Malthus, who argued that war, famine, and disease were beneficial for those who survived, by decreasing the competition for limited resources, became a near equivalent to the catastrophic floods that the creationists had invoked to explain the geological record that contained evidence of many extinct animals. The doctrine of Malthus, like that of the Catastrophists, made loss, deletion, and destruction into a central device for explaining the history of the world.

Both of the Darwins had accepted the idea that many biological changes were adaptive, rather than random, but the new practical compromise doctrine introduced the idea that changes were just "random variations." The essentially mechanical nature of the world was preserved, because "chance" occurrences could be dealt with, and didn't involve anything supernatural. The function of the environment wasn't to add anything to life (that would have been to assert that there were creative powers other than those of the Creator), but simply to eliminate the inferior individuals that appeared as the result of random changes.

Gregor Mendel applied the principle of chance to explaining the inheritance of certain traits, and showed that "traits" were passed on unchanged, even when they weren't visible. His ideas were published and were acceptable to the scientific mainstream of his time. Traits were determined by "factors" that were passed on, unchanged, from parents, and biological variation was explained by varied mixing of factors which in themselves were unaffected by the organism or the environment. Genetic determinism was safely compatible with creationism.

Shortly after Mendel's death, August Weismann began a campaign to put a stop to the claims of those who, like the Darwins and Lamarck, saw adaptive development of organisms as an essential part of the evolution of species.

Weismann was essentially a propagandist, and his first fame was the result of "disproving" Lamarck by cutting the tails off more than 1500

mice, and observing that their offspring were born with tails. The reason the inheritance of acquired traits was impossible, he said, was that the "germ line" was perfectly isolated from the rest of the organism. The differentiated tissues of the body were produced by the selective loss of information from the nuclei of cells in the embryo. The cells of the germ line were immortal and contained all the information needed to produce an organism, but no other cell of the organism was complete.

Complexity was produced by deletion, and this was the basis for arguing that, if even the development of an individual was nothing but a passive unfolding of inherited properties, much like unpacking a trunkful of clothes, then there could be no adaptively acquired traits, and certainly no inheritance of something which didn't exist. Changes in an individual were simply accidents, such as having a tail amputated, and so the whole issue of the origin of complexity was safely left to a primordial creation.

Weismann and his arguments were famous in Europe and the U.S., and formed the background for the ideas known as neo-Darwinism. His "isolation of the germ line" was the earliest version of the Central Dogma of molecular biology, namely, that information flows only from DNA to RNA to protein. His doctrine, of complexification through deletion, is the epitome of the greatest dogma of modern times, expressed in doctrines from Catastrophism through the second law of thermodynamics and the theory of the Big Bang, down to Hayflick's Doctrine of the mortality of somatic cells. All these are consequences of the Cartesian and Deistic separation of intelligence from matter.

Regeneration is one of the most vivid examples of the intelligence of living substance.

Given a natural tendency of cells to multiply, the interesting thing about regenerative healing is the question of why the new growth of tissue sometimes differentiates to fit appropriately into its surroundings, but sometimes fails to differentiate, becoming a tumor.

With aging, the regenerative process declines, and the process of tissue rebuilding slows. Against a background of reduced regenerative ability, tissue growth sometimes produces tumors, rather than renewed healthy tissue. When tumors are grafted onto the amputated tail stump of a salamander, which has good regenerative ability, the tumor is transformed into a tail, by its environment, or morphogenic field. The "cancer problem" is essentially the problem of understanding the organizing

forces of the organism. The aging problem is another aspect of the same problem.

Traditionally, biologists had studied anatomy, physiology, embryology or development, and taxonomy or the classification of organisms. The growth of knowledge early in the 20th century was suddenly seeming to confirm the physiological, adaptive view of organisms that Lamarck had held. C. M. Child, Joseph Needham, Alexander Gurwitsch, and L. V. Polezhaev were demonstrating the primacy of a formative process in biology. Polezhaev and Vladimir Filatov were studying practical means of stimulating regeneration as a medical technique.

Until the beginning of the second world war, the study of regeneration and the pattern-forming processes in embryology were the liveliest parts of biological research. Gestalt psychology was being developed at the same time, with a similar emphasis on patterns and wholes.

But Weismannism and neo-Darwinism, largely embodied in the person of the geneticist T. H. Morgan, deliberately set out to kill that line of biological research. Gestalt psychology was similarly eliminated by the Behaviorists.

One of Morgan's closest associates, his student and colleague A. H. Sturtevant, said that "Morgan's objectives, what he was trying to get at in general in his biological work was to produce mechanistic interpretations of biological phenomena. One of the things that irritated him most was any suggestion of purpose in biological interpretation. He always had some reservations about the idea of natural selection, because it seemed to him to open the door to interpretations of biological phenomena in terms of purpose. He could be talked into the conclusion that there was nothing that wasn't strictly mechanistic about this interpretation, but he never liked it. And you had to talk him into it again every few months."[1]

Whatever his motives, Morgan was known to have prevented his students (including C. M. Child) from publishing work that supported a holistic view of the organism. After Morgan's death, there was an intense and widespread campaign to suppress any approach to biology other than the "new synthesis," neo-Darwinism, with its doctrine of mechanistic genetic determinism and its doctrine of random variation. A developmental biologist, J. M. Opitz,[2] commented that "in one of the most astounding developments in Western scientific history, the gradient-field, or epimorphic field concept, as embodied in normal ontogeny and

as studied by experimental embryologists, seems to have simply vanished from the intellectual patrimony of Western biologists."

Formative processes are necessarily multidimensional, and that makes calculation and analysis very complex. To a great extent, the geneticists were motivated to study bacterial genes, rather than vertebrate embryos, by the principle that motivated the drunk to look for his car keys under the street lamp, even though that wasn't where he lost them, because the light made it easier to look there.

Bacteria are easy to study because they lack the complexity that makes it hard to study an embryo or an animal. The language used in genetics textbooks shows not only that bacteria are treated by geneticists as if they were one or two dimensional, but that the concepts developed for bacterial genetics have been extrapolated to use in describing complex organisms: "Genes interact to establish the body axis in Drosophila. Homeotic Genes control pattern formation along the anterior-posterior body axis."[3]

One of the basic distinctions in embryology is in the way the cells divide after the egg is fertilized. Oysters and earthworms have spiral cleavage, sea urchins and people have radial cleavage. Several decades ago an experimenter was transferring a nucleus from an egg of an animal with radial cleavage, I think a sea urchin, into the enucleated egg of a snail, with spiral cleavage. The nucleus transplanted across such a great difference in phyla didn't sustain maturation of the animal, but it did permit development to proceed for several rounds of cell division, and the pattern of cell division, or cleavage, and embryonic development always followed the pattern of the phylum to which the egg cytoplasm belonged, never the pattern of the phylum from which the nucleus was derived. The genes in the nucleus, obviously, weren't directing the basic pattern formation of the embryo.

One-dimensional bacterial genetics can be used to "explain" multidimensional systems, but it can't be expected to make useful predictions.

The idea of complexity, or of multidimensionality, has often been analyzed in terms of "fields," by analogy with a magnetic field, as some property, or properties, that extend beyond any individual part, giving some coherence to the parts. Lamarck was concerned with understanding ensembles of particles and cells, but in his time electricity and heat were the only principles that physics provided that helped to illuminate the nature of living organisms. At the end of the 19th century, though,

the physicist J. C. Bose was noticing that all of the properties of life that had interested Lamarck and Buffon—irritability, sensation, contraction, memory, etc.—had their close analogs in non-living substances. Bose, who invented the radio detector that was the core of Marconi's apparatus, found that, in the presence of an electromagnetic field, particles of a substance, such as finely powdered metal filings, cohered into a unified whole. An otherwise invisible, undetectable "field" which in Lamarck's time might have been known as one of the "subtle fluids," was able to organize a myriad of inert particles into a unified whole.

In the early 1920s, Bungenberg de Jong and A.I. Oparin showed how solutions of organic substances could spontaneously organize themselves into complex systems, with differentiated parts. A Russian embryologist, Alexander Gurwitsch, found that the parts of an organ or embryo could exert their stimulating or organizing influence on other cells even through a piece of glass, and by using different types of filter, he identified ultraweak ultraviolet rays as a medium of communication between cells. F.-A. Popp and others are currently studying the integrating functions of ultraweak light signals. Guenter Albrecht-Buehler (who has an interesting website called Cell Intelligence) is investigating the role of pulsed infrared signals in cell communication.

Electrical fields produced by cells, tissues, and organisms have been shown to influence cellular metabolism and physiology, and to influence growth patterns. Closely associated with cellular electrical fields are fields or gradients of pH and osmolarity, and all of these fields are known to affect the activity of enzymes, and so to create environments or fields of particular chemical concentrations.

A phenomenon that was well known in the 1930s, when developmental fields were still a familiar part of scientific discussion, was the "cancer field." Before a cancer developed in a particular area, the area showed progessive changes, away from normal function and structure, toward the cancer physiology.

In the embryonic state, damaged tissues regenerate quickly. The metabolism of an embryo or fetus is highly oxidative, converting glucose rapidly to carbon dioxide and water. Both carbon dioxide and water are important regulators of cellular metabolism and function, and the concentrations of both of them decrease systematically with maturity and aging. Both are involved with the most basic aspects of cellular sensitivity, responsiveness, and organization.

To resume the scientific tradition that has "simply vanished," I think we have to recover our ability to think about organisms generally, leaving aside as many of the concepts of genetics as possible (such as "gene," "operon," "receptor"; "the gene" has never been more than an ideological artifact), because they so often falsify the most important issues. The organization of tissues and organs, and their functional properties, should be the focus of attention, as they were for Lamarck around 1800, and for Johanes Muller, who in 1840 saw cancer as a problem on the level of tissue, rather than cells. For Lamarck, sensitivity and movement were the essential properties of the living substance, and J. C. Bose showed reasons for believing that the characteristics of life were built on related properties of matter itself.

Sensitivity, the ability to respond appropriately to the environment, is probably a missing factor in the development of a tumor. The ability to become quiescent, to quietly participate in the ensemble of cells, is an essential feature of the sensitivity and responsiveness of the cells of complex organisms. The factors that support organized appropriate functioning are the factors that help cells to inhibit the excitatory state. If the keys of an accordion or organ didn't spring back after the musician pressed them, the instrument would be unplayable. In extreme physiological states, such as epilepsy or malignant hyperthermia, nerves or muscles become incapable of relaxing. Insomnia and muscle cramps are milder degrees of a defective relaxation process. Excitoxicity and inflammation describe less generalized cases of a similar process, in which there is an imbalance between excitation and the restorative ability to stop the excitation. Prolonged excitation, resulting in excessive fatigue, can cause a cell to disintegrate, in the process of cell death called apoptosis, "falling away."

In the experiments of Polezhaev and Filatov, the products of cell disintegration were found to stimulate the birth of new cells (possibly by blocking a signal that restrains cell division). This process has been found in every organ that has been examined appropriately. It amounts to a "streaming regeneration" of the organism, analogous to the progressive creation of Lamarck's view. G. Zajicek has demonstrated an orderly "streaming" renewal in several organs, and even the oocytes (which in the Weismannian dogma were formed at a very early stage during embryonic development, and were perfectly isolated from the cells of the

mature body) have recently been shown to be continually regenerated in adult ovaries.

"Stem" cells turn out to be ubiquitous, and the failure of regeneration and restoration seems to be situational. In the 1950s a magazine article described the regeneration of a finger-tip when the wound was kept enclosed. Decades later, friends (one a child, the other a man in his forties) had accidental amputations of a finger-tip, down to the cuticle so that no visible nail remained. The boy's mother fitted his finger with the tube from a ballpoint pen, and the man used an aluminum cigar tube as his "bandage." Within a few weeks, their fingers had regenerated to their normal shape and length. I think the closed environment allows the healing tissues to be exposed to a high concentration of carbon dioxide, in equilibrium with the carbon dioxide in the capillaries, and to a humid atmosphere, regulated by the osmotic or vapor pressure of the living tissues.

Under ordinary conditions, the creation of cells and the dissolution of cells should be exactly balanced. The coordination of these processes requires a high degree of coherence in the organism.

Simple increase of water in the vicinity of a cell increases its tendency to multiply, as well as its excitability, and hypertonicity restrains cell division, and reduces excitability. Carbon dioxide, besides helping proteins to release water, appears to increase the ability of proteins and cells to respond to morphogenetic fields. Carbon dioxide is the most universal agent of relaxation, restoration, and preservation of the ability of cells to respond to signals. Progesterone is another very general agent of restorative inhibition.

The study of regeneration and "stem cells" is helping to illuminate the general process of aging, and to provide very practical solutions for specific degenerative diseases, as well as providing a context for more appropriate treatment of traumatic tissue injury.

In aging, the growth and regenerative processes are slowed. There is some evidence that even cell death is slower in old age, at least in some tissues. Since animals with the highest metabolic rate live the longest, the slowing rate of metabolism during aging probably accounts for those changes in the rate of cell renewal. The continually streaming regeneration of tissues is part of the adaptive process, and it is probably intensified by stress.

The ability to sleep deeply decreases in old age, as a generalized inflammatory, excitatory state of stress develops. With progressive weakening of restorative cellular relaxation (inhibition), cells become more susceptible to disintegration. It's well established that bone loss occurs almost entirely during the night, and since the catabolic hormones generally affect soft tissues as well as bones, the atrophy of soft tissues ("sarcopenia") of aging is also probably a process that occurs mostly during the night. Mediators of inflammation are at their highest during the night.[4] But during the period of growth, the length of bones seems to increase mostly during the night.[5] My interpretation of this is that the stress of darkness accelerates biological processes, whether the process is mainly constructive or mainly destructive.

The effect of light supports efficient oxidative energy production, which supports the protective inhibitory processes, by increasing ATP and CO_2, and decreases the inflammatory mediators that intensify stress. If organized cellular luminescence is required for a proper balance, then the random luminescence produced by lipid peroxidation (which may be more intense at night[6]), might be an important factor in disrupting the balanced streaming of regeneration. Free radicals, whatever their source, absorb a broad spectrum of radiation, and would block luminous signals of all frequencies. Isoprene, produced mainly at night,[7] is another ultraviolet absorber that might account for nocturnal regulatory disorders.

The age pigment, lipofuscin, is known to contribute to degenerative diseases, but the nature of its toxicity has never been established. Its absorptive and fluorescent properties would be very likely to interfere with mitogenetic and morphogenetic radiation. Polyunsaturated fats are the main component of lipofuscin, and these fats in themselves can absorb ultraviolet light. When those fats are present in the skin, exposure to ultraviolet light accelerates the aging of the skin. Free fatty acids often increase during the night, under the influence of hormones such as adrenaline and growth hormone.

A single night of poor sleep probably causes significant anatomical damage to the streaming cellular systems that will be repaired over the next few days if a high level of energy metabolism can be combined with a sufficient amount of deep sleep. The things that optimize energy and sleep form the background for supporting the restorative processes. Salt, glycine, carbon dioxide, progesterone, thyroid hormone and sugar all

contribute to preserving the organism's energetic reserves by reducing inappropriate excitation.

Lamarck's idea that organs developed or regressed according to their use or disuse was often attacked by followers of the Weismann-Morgan genetic dogma. In their view, the influence of the environment was limited to either preventing or permitting the realization of "the genetic potential." Once that predefined potential had been unfolded, the finite and mortal nature of the somatic cells didn't allow for any significant changes, except for depletion and death. One of the high points of Weismannian biology came with the publication of an article in Science, around 1970, that proposed to explain learning in terms of the lifelong loss of brain cells, beginning in humans around the age of 18 months, with a daily loss of 100,000 cells, which would record experience by selective deletion, the way punching holes in cards had been used to enter data into computers. I was present to witness "world class biologists" taking that idea very seriously.

As Sturtevant mentioned in the quotation above, T.H. Morgan couldn't accept any attribution of purposefulness to organisms. In his genetic dogma, changes were only random, and people who denied that were denounced as "teleological" (or metaphysical) thinkers. Changes occurred by deletion, not by meaningful addition.

One of Pavlov's students, P. K. Anokhin, developed the concept of the Functional System in the 1930s, to explain the purposive behavior of animals. In the 1950s, Anokhin integrated the endocrinology of stress and adaptation into the concept, and F. Z. Meerson continued the work, concentrating on the metabolic and structural changes that protect the heart during stress. The simplest view of the conditional reflex involves the adaptation of an animal to an external signal, identifying it as the occasion for a particular action. Analyzing the Functional System starts with the need of the animal, for example for food, and examines the processes that are involved in satisfying that need, including nerve cells, a sense of hunger, knowledge of what things are edible, the muscles needed to get the food, and the digestive apparatus for assimilating it.

When an understanding of stress physiology is combined with the idea of functional systems, the adaptive meaning of the use or disuse of certain organs is given a concrete basis. Cortisol mobilizes amino acids from muscles that are idle, and makes them available for the synthesis of proteins in the muscles, nerves, or glands that are activated in adapting

to the stress. The London taxi drivers whose hippocampus grows as they learn the locations of the streets are very good examples of the processes described by Meerson, Anokhin, and Lamarck, in which the use of an organ in meeting a need contributes to the development of that organ. The balance between growth and regression is shifted during adaptive behavior.

Exercise physiologists, without mentioning functional systems, have recently discovered some principles that extend the discoveries of Meerson and Anokhin. They found that "concentric" contraction, that is, causing the muscle to contract against resistance, improves the muscle's function, without injuring it. (Walking up a mountain causes concentric contractions to dominate in the leg muscles. Walking down the mountain injures the muscles, by stretching them, forcing them to elongate while bearing a load; they call that eccentric contraction.) Old people, who had extensively damaged mitochondrial DNA, were given a program of concentric exercise, and as their muscles adapted to the new activity, their mitochondrial DNA was found to have become normal.

There are probably the equivalents of constructive "concentric" activity and destructively stressful "eccentric" activity in the brain. For example, "rote learning" is analogous to eccentric muscle contraction, and learning by asking questions is "concentric." "No bird soars too high, if he soars with his own wings." Any activity that seems "programmed" probably stifles cellular energy and cellular intelligence.

When activity is meaningful, and is seen to be meeting a felt need, the catabolic and anabolic systems support and strengthen the components of the functional system that has been activated. Everything we do has an influence on the streaming renewal of the adaptive living substance.

There are many therapeutic techniques that could be improved by organized research, for example, investigating the interactions of increasing carbon dioxide, reducing atmospheric pressure, supplementing combinations of salt and other minerals, balancing amino acids and sugars, and varying light exposure and types of activity. The dramatic results that have occasionally been demonstrated (and then suppressed and forgotten) are just a hint of the possibilities.

If we keep our thoughts on the living substance, the pervasive ideologies lose their oppressive power.

Aging, Estrogen, and Progesterone

Ray Peat's Newsletter, 2006

THE balance between what a tissue needs and what it gets will govern the way that tissue functions, in both the short term and the long term. When a cell emits lactic acid and free radicals and the products of lipid peroxidation, it's reasonable to assume that it isn't getting everything that it needs, such as oxygen and glucose. With time, the cell will either die or adapt in some way to its deprived conditions.

In aging, tissues generally atrophy, with loss of both substance and activity. Ordinarily, organisms react to stress with increased activity of the appropriate functional system, but when the stress is inescapable, organisms adopt the strategy of decreasing their demands, as in hibernation or the defensive inhibition that has been called parabiosis, the state of being "not fully alive." In many situations, serotonin (which is closely associated with estrogen) seems to be an important inducer of this state. There are many indications that estrogen is a factor[1,2] in functionally suppressed states such as hibernation, social subordination, learned helplessness and depression. Social subordination in animals often involves high estrogen and reduced fertility.

In good health, an animal's systems are designed so that certain tissues will be intensely but briefly stimulated by estrogen. This stimulation by estrogen doesn't produce the normal amount of carbon dioxide, so the tissue experiences oxygen deprivation, leading to swelling and cell division. (Along with the reduced carbon dioxide production, there is increased lipid peroxidation). Any similar stimulation, whether it's produced by soot, or suffocation, or irradiation, will produce the broad range of estrogen's effects, beginning with inflammation but ending with atrophy or cancer if it is too prolonged.

Although, as the 21st century begins, the U.S. government hasn't decided whether to classify estrogen as a carcinogen, it was identified as a carcinogen in the first half of the 20th century—and a variety of carcinogens were found to be estrogenic.

Many people studying estrogen's biological effects observed that certain of its effects resembled the changes seen in aging, such as fibrotic changes of connective tissues, accelerated accumulation of age pigment, a tendency to miscarry, or the production of degenerative

changes in various organs. But as far as I know, I was the first one to suggest that aging itself involves increased estrogen dominance. (Taking this perspective suggests many specific things to do for aging. And, if radiation injury, and stress, are "estrogenic," it suggests that specific anti-estrogenic treatments could be appropriate.) I based my argument on the identity of the biochemical and tissue effects produced by aging and by estrogenic excess. At that time, techniques for the accurate measurement of very small amounts of estrogen hadn't been fully developed. I felt that the situation should have been clear, because of the previous decades of research, and I used that as the context for arguing that the reason for age-related infertility was the same as for estrogen-induced infertility or stress-related infertility, namely, the inability to deliver oxygen to the embryo. I thought of the developing embryo as a sensitive indicator of processes that occur throughout the body during aging and stress, and that the destruction of the embryo by the excessive estrogen of the birth control pill was closely analogous to the progressive loss of function that occurs in so many tissues during normal aging.

After I wrote my dissertation, Terry Parkening, who had worked in the same lab, sent me data from rats, showing that his measurements confirmed the increase of estrogen with aging. Since then, many others have shown that either the absolute levels of estrogen, or the ratio of estrogen to the antiestrogens, increases with aging in a wide variety of organisms of both sexes, including humans.

In the 1970s, the claims about estrogen curing osteoporosis apparently had been debunked. At the time, that appeared to be the last of the major claims for the therapeutic properties of estrogen. Studies in dogs were starting to show that estrogen was an important cause of degenerative bone disease, as well as kidney disease, liver disease, thyroid disease, etc. Hormones used in contraceptives were producing cancer in dogs, as well as many other diseases, so dog research was widely abandoned by the drug industry/FDA, in favor of animals that were less sensitive, or differently sensitive, to the hormones. The claims that the industry was making were contradicted by the dog research, so they sought new animal "models" that wouldn't so clearly contradict their claims.

A great advantage, for the drug industry, of using rats instead of dogs is that expensive, and often embarrassing, long-term experiments aren't possible in such short-lived animals. Rats die when their tissues

still appear to be relatively young. Although excess prolactin (resulting from excess estrogen) in humans is an important cause of osteoporosis, in rats at a certain age and on a certain diet, hyperprolactinemia can stimulate bone growth.[3,4] This trait of rats could be very advantageous to the estrogen industry.

All of the maladies caused by estrogen excess appear to develop in the same way that it interferes with pregnancy, by driving the tissue to require more energy and oxygen than can be delivered to it. Necrosis, the death of sections of tissue, was produced acutely by extreme overdoses of estrogen, or gradually by less extreme overdoses, and if the estrogenic stimulation was milder but very prolonged, the result would usually be tumors, sometimes developing in the midst of atrophy or necrosis. An overdose of estrogen was used to shrink breasts and prevent lactation, and an even larger dose was used to kill breast tissue in treating cancer. A recent study[5] shows that, at least in women, estrogen is closely associated with the general loss of fat-free tissue with aging. This shows a close association between the generalized atrophy of aging and the amount of estrogen in the tissues.

In the case of the embryo that can't implant in the aged or estrogenized uterus, it is because oxygen is being consumed so fast by the uterus that very little is available for the embryo. The uterus is, effectively, in an inflamed state, and the embryo is in a state that requires abundant oxygen. The general loss of tissue that Toth associated with increased estrogen follows many of the same steps that occur in the failure of the embryo to implant in the uterus: Glycogen is depleted in futile oxidative cycles, protein synthesis is inhibited, lipid peroxides and free radicals accumulate, cellular defensive and repair processes replace normal functioning.

(With aging, the loss of glycogen in the brain has serious consequences, including insomnia. Estrogen's depletion of glycogen in other tissues is probably important for their functioning, and thyroid and progesterone are known to help maintain the glycogen stores.)

In the last several years, according to the medical literature estrogen would seem to have outgrown nearly all of its bad traits. It protects the brain, the heart, the blood vessels, even the fetus, and it prevents many kinds of cancer, and improves memory, mood, and immunity. And it would still seem to be of great promise in treating breast cancer and prostate cancer, if we took some medical journals seriously. It

achieves many of these nice things by functioning as an antioxidant and by increasing circulation, often acting through nitric oxide and serotonin or melatonin. Even though I have read thousands of the articles that said otherwise, the near unanimity of the current research literature can almost give me the feeling that things might not be exactly as they had seemed.

In fact they aren't, but the change is in what passes for science, rather than in the way organisms respond to estrogen. Many little pictures are being presented, that seem to add up to a very different big picture. It is clear that this new picture is being painted by those who fund the research, and by some of those whose careers depend on that funding. The people who do the odd little studies of estrogen and cytokines, nitric oxide, regulatory genes, and so on, are usually getting the data they claim to get, and if they draw speculative conclusions about what their study means medically, that's their privilege. But hundreds of these little publications that would be harmless individually, add up to national policy endorsed by the FDA and other powerful agencies—they add up to the same sort of criminal conspiracy that the tobacco industry and its researchers perpetrated throughout the twentieth century.

Journals that are considered to be the best in their field publish many papers that simply misrepresent some of the basic facts, while interpreting experimental results that would otherwise have unpleasant commercial implications.

For example, the follicular phase is a time of low steroid production by the ovary, until near the end of the phase, just before ovulation, when estrogen rises. The luteal phase is a time of high estrogen and high progesterone synthesis. Many publications describe the follicular phase as a time of high estrogen, and the luteal phase as a time of low estrogen, roughly the opposite of the actual situation. And an even larger number of studies get the results they want by using a short exposure to estrogen to study something which takes a long time to develop.

In the last few years, one of the most common tricks of estrogen promotion is to argue that estrogen protects against heart disease and Alzheimer's disease because it relaxes blood vessels, by increasing the formation of nitric oxide. It does generally increase the formation of nitric oxide, but nitric oxide is a toxic free radical that plays a major role in degenerative diseases. And the inappropriate relaxation of blood

vessels, coupled with increased clottability of the blood, is a major cause of pulmonary embolisms and venous disorders.

In studies of tendons, excess estrogen, aging, and cooking (the phenomenon of the curling pork chop) all caused hardening and contraction of the collagen. When people get to be 90 or 100 years old, the opening between their eyelids is sometimes contracted, presumably because of this process of collagen shrinkage. If this shrinkage of connective tissue affects the large blood vessels, they become narrower and stiffer, so that the blood has to travel faster if the same amount is to be delivered in the same time.

Ultrasound can be used to measure the velocity of the blood flow, and increased velocity will correspond to constriction of the channel, if the same amount of blood is being delivered. But many people praise estrogen's vascular benefits on the basis of tests showing increased blood velocity in large arteries such as the aorta, without evidence that more blood is being circulated. With aging, as arteries become constricted, increased blood velocity is taken as evidence of the pathology. Velocity measurements have to be interpreted in the contexts of tissue perfusion, cardiac output, etc. When the diameter of the artery is considered along with the velocity of the blood, the volume of flow can be determined, and then it appears that progesterone increases blood flow, while estrogen can decrease it.[6] This would be consistent with the known ability of an estrogen excess to cause retarded growth of the fetus, as well as specific birth defects.

Estrogen does increase the blood flow to particular organs, but apparently less than it increases their oxygen demand, as can be seen from the color change of estrogenized tissues, toward purple, rather than pink. Measurements of oxygen tension in the tissue show that estrogen decreases the relative availability of oxygen. And when the level of estrogen is very high, metabolically demanding tissues, such as the kidney and adrenal cortex, simply die, especially under conditions that restrict blood flow.[7–9] When estrogen's effects overlap with the stimulating effects of other hormones, such as pituitary hormones, particular organs undergo something similar to "excitotoxicity." When estrogen overlaps with endotoxin (as it tends to do), multiple organ failure is the result.

The simple need for more oxygen is a stimulus to increase the growth of blood vessels, and estrogen's stimulation of non-mitochondrial oxygen

consumption with the production of lactic acid stimulates blood vessel formation. Progesterone, by increasing oxidative efficiency, opposes this "angiogenic" (neovascularization) effect of estrogen.

Szent-Györgyi spent most of his career studying muscles—from the anal sphincter to pigeon breast to tense goats. One of his most interesting experiments investigated the effects of estrogen and progesterone on the heart muscle. He showed that estrogen excess prevents the increase of stroke volume as the speed increases, but that progesterone increases the stroke volume as the heart accelerates, making pumping more effective without unnecessary acceleration of the heart rate. These effects are parallel to Selye's observation that estrogen imitates the shock reaction.

In shock, the blood pressure decreases, mainly because the blood volume decreases. Water is taken up by the tissues, out of the blood. Much of the remaining blood volume is accumulated in the relaxed veins, and little is returned to the heart, yet the increased need for circulation accelerates the heart, causing each stroke to pump only a small amount. The reduced blood pressure caused many people to think that adrenaline would help to improve the circulation, but actually the "resistance arteries," small arteries that provide blood to the arterioles and capillaries, are constricted in shock,[10] and adrenaline usually makes the situation worse. When tissue is poorly oxygenated (or is exposed to estrogen) it takes up water, swelling and becoming more rigid, turgid. (It also takes up calcium, especially under the influence of estrogen, causing muscles to contract.) This swelling effect will be much more noticeable in small arteries than in major arteries with very large channels, but when the effect is prolonged, it will affect even the heart, causing it to "stiffen," weakening its ability to pump. There is some evidence that estrogen can make large arteries stiffen, over a span of a few months.[11]

Estrogen, by creating an oxygen deficiency, stimulates first swelling, and then collagen synthesis. Collagen tends to accumulate with aging.

In shock, the cells are in a very low energy state, and infusions of ATP have been found to be therapeutic, but simple hypertonic solutions of glucose and salt are probably safer, and are very effective. The low energy of cells causes them to take up water, but it also causes the veins (which always receive blood after most of its oxygen and nutrients have been extracted) to lose their tone, allowing blood to pool in them, instead of returning to the heart.[12] This contributes to varicose veins,[13] and to

orthostatic hypotension, which is seen in women who are exposed to too much estrogen, and very frequently in old people.

The energy failure resulting from estrogen excess has been remarkably well characterized (but the meaning of this for the cell hasn't been explored). The electron transfer process of the mitochondria is interrupted by the futile redox cycling catalyzed by estrogens.

Good sleep requires fairly vigorous metabolism and a normal body temperature. In old age, the metabolic rate is decreased, and sleep becomes defective. Protein synthesis declines with aging, as the metabolic rate slows. At least in the brain, protein synthesis occurs most rapidly in deep sleep.[14,15]

In old age, the catabolic hormones such as cortisol are relatively dominant,[16] and even in youth, cortisol rises during darkness, reaching its peak around dawn. Even in young women, bone loss occurs almost entirely during the night, when cortisol is high. The hormones that are commonly said to prevent bone loss, estrogen and growth hormone, are high at night, rising along with cortisol. Estrogen causes growth hormone to increase, and in the morning, young women's growth hormone has been found to be 28 times higher than men's.[17] The growth hormone response to estrogen is probably the result of the changed use of glucose under estrogen's influence, making it necessary to mobilize free fatty acids from tissues. While estrogen is usually highest at night, progesterone is lowest during the night. These observations should suggest that progesterone, not estrogen, is the bone protective substance.

The disappearance of water from the blood, as it moves into the tissues during the night, makes sleep resemble a state of shock or inflammation. Since rats, that are active at night, experience the same blood thickening, it's actually the darkness, rather than sleep, that creates this "inflammatory" state. Estrogen increases, and acts through, the inflammatory mediators, serotonin and histamine, to increase vascular leakiness, at the same time that it causes cells to take up water and calcium. The formation of lactic acid, in place of carbon dioxide, tends to coordinate these effects.

In sleep, as in shock, hyperventilation is common, and it sometimes produces extreme vasoconstriction, because of the loss of carbon dioxide.

Since glucose and salt are used to treat shock (intravenous 7.5 % salt solutions are effective), it seems appropriate to use carbohydrate (preferably sugar, rather than starch) and salty foods during the night,

to minimize the stress reaction. They lower adrenalin and cortisol, and help to maintain the volume and fluidity of blood. Thyroid, to maintain adequate carbon dioxide, is often all it takes to improve the blood levels of salt, glucose, and adrenalin.

Temperature falls during sleep. Recent experiments show that hypothermia during surgery exacerbates the edema produced by stress, and that hypertonic (hyperosmotic or hyperoncotic) solutions alleviate the swelling. It is possible that light's action directly on the cells helps them to prevent swelling, and that the body's infrared emissions have a similar function. Whatever the mechanism is, adequate temperature improves sleep, and an excessive nocturnal temperature drop probably increases edema, with all of its harmful consequences.

At least some of the redox cycles involving NAD/NADH and NADP/NADPH keep electrons from moving beyond ubiquinone (CoQ_{10}) and energizing the mitochondria. The cycle that makes nitric oxide is one of these, but some forms of estrogen participate directly as catalysts in this energy-stealing process. One of the effects of blocking electron transfer in the mitochondria is to lower the energy charge of the cells, mimicking the function of the age-damaged mitochondria. Glutathione and protein sulfhydryls are oxidized, because the normal energy pathways that maintain them have been disrupted.

Estrogen directly lowers the temperature, while progesterone raises the temperature. Estrogen sets the brain's temperature regulator lower, but, acting through serotonin and other mediators, it can actually lower the metabolic rate, too.

Far from being just the "hormone of estrus," estrogen, in the form of estradiol and the related steroids, plays a role in organisms as diverse as yeasts, worms and mollusks, and in modifying the function of practically every type of animal cell—skin, nerve, muscle, bone, hair, gland, etc. But, as more and more of its functions come to be understood, it turns out that many toxic chemicals and stressful physical processes can activate the same functions, and that estrogen's association with the functions of stress makes it a kind of window into some universal biological functions.

When Hans Selye brought it to our attention that "stress" was a general life process, he began a process of generalization that led people to be able to see that the changes of aging were also the result of complex interactions between organisms and their environment, rather than some genetic program that operates like a clock running down.

When W. Donner Denckla demonstrated that the removal of an animal's pituitary (or, in the case of an octopus, its equivalent optic gland) radically extended the animal's life span, he proposed the existence of a death hormone in the pituitary gland. But the case of the octopus makes it clear that the catabolic, death-inducing hormone is produced by the ovary, under the influence of the optic gland's gonadotropins. This sacrifice of "the old" (the individual) for "the new" (the progeny) is analogous to the tissue wasting we see under the influence of estrogen, as it stimulates cell division.

In Selye's classical stress, the destruction of tissues by the catabolic hormones makes sense in terms of the "functional system" described by Anokhin, in which the hormones of adaptation dissolve one tissue for use by the system which is adaptively functioning, with the production of carbon dioxide by the functional tissue, stabilizing it and regulating the adequate delivery of blood.

Progesterone is both an anticatabolic hormone and an antiestrogenic hormone, and in both cases, it protects the functional systems from atrophy.

The extreme generality of the phenomenon of "estrogenicity" that was built up during the twentieth century has taken the concept beyond the specific functions of estrus, and reproduction, and the activation of genetic programs of the female animal, to make it necessary to see it as a way that living substance responds to certain kinds of stimulus. And these ways of responding turn out to be involved in the complex but coherent ways that organisms respond to aging.

Selye gave various names to the biology of stress, but the "general adaptation syndrome" expressed the idea accurately. But the biology of estrogenicity, like the biology of aging, is so central that any name is likely to be misleading. The historical accident of naming a hormone for estrus shouldn't keep us from thinking about the way estrogen affects our energetics and structure, and how those processes relate to aging, atrophy, cancerization, etc.

While progesterone is probably the most perfect antiestrogenic hormone, and therefore an anti-stress and anti-aging hormone, the recognition of a wide variety of estrogen's effects has made it possible to adjust many things in our diet and environment to more perfectly oppose the estrogenic and age-accelerating influences.

Aging Eyes, Infant Eyes, and Excitable Tissues

Ray Peat's Newsletter, 2006

One of the recognized achievements of biology has been the demonstration of life's universality, in the sense that organisms of all sorts use the same fundamental genetic code, and that yeasts, lizards, apes, and people have remarkably similar cellular systems, as well as a great amount of genetic similarity.

There has been another, less well recognized, sort of convergence going on in physiology and pathophysiology. Hans Selye's concept of stress, "the syndrome of being sick," Otto Warburg's argument that a "respiratory defect" was behind all kinds of cancer, and the idea of free radical damage as a common factor in disease and aging, helped to create a more general way of looking at the nature of disease that superceded medicine's theories of disease pathogens and genetic mutations, which created thousands of "disease entities," none of which had much to do with the individuality of the patient or his environment.

The understanding that plants and animals have much biochemistry in common has gradually changed the assumptions of the science establishment, which until recently insisted that only "ionizing radiation" could affect animals or other organisms that lacked chlorophyll—and insisted that ionizing rays acted only on the DNA. Visible light, the textbooks said, was not "chemically active," and so couldn't possibly affect animals' cells. In animals, coloration was seen mainly as decoration and disguise, rather than as a functional part of their biochemistry.

(Chemically, the meaning of "a pigment" is that it's a chemical which selectively absorbs radiation. Old observations such as Warburg's, that visible light can restore the activity of the "respiratory pigments," showed without doubt that visible light is biochemically active. By the 1960s, several studies had been published showing the inhibition of respiratory enzymes by blue light, and their activation by red light. The problem to be explained is why the science culture simply couldn't accept crucial facts of that sort.)

The retina, of course, was allowed (in the views of mainline science) to respond to ordinary light, but the few people who studied the biological effects of seasonal or daily cycles of light have until recently stayed very close to the nerve pathways leading from the retina to the

pineal gland, because those pathways could be described in terms of an evolutionarily specialized "third eye." Even with a doctrine of a genetically specialized link between the retina and a little of the animal's physiological chemistry, the great, slow-witted science establishment has done its best to avoid thoughts of any deep interaction between an organism and its environment, by insisting that the organism runs according to a genetically determined "clock" which is located in a few cells in a certain area of the brain, and that nervous impulses from the retina have only the small privilege of "setting the clock."

It didn't matter to the academic and medical worlds that a professor, Frank A. Brown, had long ago disproved the idea of an innate genetic "clock," because philosophy is much stronger than evidence. Leibniz had said that everything in the world runs on its own inner clock, without needing to perceive its surroundings, and this idea that everything in the world is a "windowless monad" resonated through the world of science, because it justified the pompous authoritarian attitudes of the experts who knew that anything that wasn't already in their heads couldn't be considered knowledge. If an organism's "essence is contained in its genes," then it clearly doesn't interact in any meaningful way with most of its environment. This is the sort of culture that imbued research on the biology of light cycles.

When I moved from Mexico, first to Montana and then to Oregon in 1966, I became very conscious of how light affects the hormones and the health. (For example, in Montana I experienced an interesting spring-time shedding of body hair.) Many people who came to cloudy Eugene to study, and who often lived in cheap basement apartments, would develop chronic health problems within a few months. Women who had been healthy when they arrived would often develop premenstrual syndrome or arthritis or colitis during their first winter in Eugene.

The absence of bright light would create a progesterone deficiency, and would leave estrogen and prolactin unopposed. Beginning in 1966, I started calling the syndrome "winter sickness," but over the next few years, because of the prominence of the premenstrual syndrome and fertility problems in these seasonally exacerbated disorders, I began calling it the pathology of estrogen dominance. In the endocrinology classes I taught at the National College of Naturopathic Medicine, I emphasized the importance of light, and suggested that medicine could be reorganized around these estrogen-related processes. If the sparrows

of Times Square mated in the winter because of the bright lights, it seemed clear that bright artificial light would be helpful in regulating human hormones.

In our lab at the University of Oregon, our hamsters would try to hibernate, even though they were in temperature-controlled laboratories with regular cycles of artificial light. (The ceiling lights provided only dim illumination inside their cage boxes, so they were probably in a chronic state of light deprivation, which probably increased their sensitivity to the weak environmental cues that Frank Brown had investigated, possibly microwaves that easily penetrated the lab walls.) During the winter, when they were infertile, I found that their thymus glands practically disappeared. The mechanism seemed to include the increase of pineal gland activity (probably increasing melatonin synthesis) in the winter, under the intensified activity of the "sympathetic nervous system" (with increased activity of adrenalin and other catecholamines), and the melatonin was apparently a signal for suppressing fertility during the stressful winter. In some animals,[1] estrogen is increased during hibernation, contributing to the reduction of body temperature.

In 1994 A.V. Sirotkin found that melatonin inhibits progesterone production but stimulates estrogen production, and it's widely recognized that melatonin generally inhibits the thyroid hormones, creating an environment in which fertilization, implantation, and development of the embryo are not possible. This combination of high estrogen with low progesterone and low thyroid decreases the resistance of the organism, predisposing it to seizures and excitotoxic damage, and causing the thymus gland to atrophy.

Cyclical exposure to melatonin can have an effect on the reproductive system opposite to that of chronic exposure, and the way exogenous melatonin is delivered to the animal can have unexpected effects on the actual amount of melatonin circulating in the blood.[2] The actual amount of melatonin in the tissues, its relation to the normal cycling of the animal, and the influence of temperature, are often disregarded in melatonin research, making it hard to interpret many of the publications.

There is a lot of talk about melatonin's function as an antioxidant, but, like so many other "antioxidants," melatonin can act as a pro-oxidant at physiologically relevant concentrations; some studies have found that it, like estrogen, increases the activity of the pro-oxidative free radical nitric oxide (which acts like melatonin on pigment cells, causing them

to lighten). The promoters of estrogen are also making claims that estrogen is a protective antioxidant, though that isn't true of physiological concentrations of estrogen, which can catalyze intense oxidations. The market culture seems to guide most research in these substances.

Almost any kind of stress increases the formation of melatonin.

In some animals, melatonin has been shown to be responsible for whitening of the hair during the winter. In some species it acts directly on the pigment cells, but in other species it seems to inhibit the action of the melanocyte stimulating hormone.

In snowy climates, it's "ecologically" rational for animals to turn white in the winter, for camouflage. But tadpoles also turn white in the dark, or under the influence of melatonin, and the biological meaning of that isn't so clear. It's possible that being white would reduce their loss of heat through radiation, but I think it is more likely that it relates to an increased ability of weak radiation to penetrate their tissues, rather than being stopped near the surface by the melanin in the skin. The absence of melanin makes them more sensitive to light. Bright light suppresses their melatonin, and makes them turn dark brown or black, and this protects them from bright sunlight.

In the retina, melatonin increases the sensitivity of the cells to dim light. It, along with prolactin, another nocturnal hormone, helps to produce dark adaptation of the eyes.

Melatonin increases the concentration of free fatty acids during the night,[3,4] so it's interesting that one of the long-chain highly unsaturated fatty acids, DHA (docosahexaenoic acid), also increases the light sensitivity of the retina.

Melatonin lowers body temperature, causes vasoconstriction in the brain, heart, and other organs, and slows reactions. An antagonist to melatonin acts as an antidepressant, reducing "behavioral despair" resulting from stress.[5] So, in the behavioral sense, melatonin reduces sensitivity, yet it increases the eyes' sensitivity to light, causing them to be injured by light that would otherwise be harmless.

Since a hibernating animal under the influence of melatonin can become very cold, the light-sensitizing function of melatonin is probably related to the biological need to be roused out of the torpor occasionally. (Hibernators apparently have to warm up occasionally to sleep in the ordinary manner.) Melatonin is said to intensify dreaming, which is part of the process of arousal from sleep.

All of the stress-related hormones increase during the night. One of the ways these hormones of darkness act is to increase the sensitivity to light, in a process that is an important adaptation for organisms in dim light. In the night, our ability to see (and respond to) dim light is increased. But dark-adapted eyes are very sensitive to injury by bright light. Light that ordinarily wouldn't harm the eyes, will do serious damage when the eyes are dark adapted.

In thinking about the effects of stress and oxygen deprivation, I read the studies demonstrating that the formation of the oxygen-wasting age pigment, lipofuscin, is increased by estrogen, by oxygen deprivation (in carp living below the ice, or even in fetuses), by metals such as iron, by x-rays, and by highly unsaturated fats.

Free fatty acids that are mobilized from storage tissues in the night and in the winter also tend to increase with aging, as the ability to tolerate stress decreases. Poor circulation and lipofuscin tend to be associated, in a vicious cycle. This means that the retina becomes easier to injure by light in old age, for some of the same reasons that the infant's retina is susceptible.

The fetus accumulates a very large amount of iron, and it absorbs melatonin from the maternal circulation. Prolactin is sometimes elevated in the newborn. Premature babies are often given extra oxygen, which tends to cause vasoconstriction by displacing carbon dioxide. Melatonin's ability to cause vasoconstriction means that stress makes supplemental oxygen more toxic. Synthetic glucocorticoids are often given to premature babies, adding to the risk of retinal damage.

When the mother has been given iron supplements during pregnancy, along with unsaturated oils in the diet, the baby is likely to be born with a vitamin E deficiency and suppressed thyroid function, increasing the probability that it will be jaundiced, leading to treatment of the jaundice with exposure to very bright light.

Although Yandell Henderson had already, in 1928, explained the need for carbon dioxide to be used with oxygen for resuscitating infants or adults, medical researchers and hospital workers could never accept the idea, probably because of a fundamental misunderstanding of the Henderson-Hasselbalch equation. Animal experiments show that supplemental oxygen, without carbon dioxide, causes vasoconstriction, reducing the tissues' supply of glucose as well as oxygen. In combination with too much light, especially blue light, it damages the retina. At

hyperbaric pressure, oxygen causes seizures, as well as damage to the lungs and other tissues.

The contribution of bright light to retinal damage in babies has been denied in several recent publications, and these articles undoubtedly provide useful material for defense lawyers to use when hospitals are sued for causing blindness. One publication based on experiments with kittens concludes that bright light does not harm the newborn's retina, but the comparison is between continuous light and intermittent light, rather than between bright light and dim light. Twelve hours of total darkness, rather than sparing the eye by reducing its exposure to light, would sensitize the eye. The only reason such appalling things can be published is that their conclusions protect the hospitals.

A few good studies of the effect of bright light on the retina, and the fact that dark-skinned people with more protective pigment in their eyes have a lower incidence of retinopathy of prematurity, make it clear that the ordinary laws of physics and chemistry actually do apply to the infant eye.

Light and stress, especially with excess iron, damage the retina when the cells contain too much PUFA, since these fats react with light and free radicals. The nocturnal/stress hormones, especially prolactin and melatonin, make the retina more sensitive to light, and more easily damaged. (It's too much darkness that sets up the problem, since the eyes will adapt to excess light, but darkness increases their sensitivity.)

The use of lasers to operate on eyes produces intense inflammation of the eye, but even at low dose the diffusing light causes retinal/macular damage.

Cytochrome oxidase is one of the enzymes damaged by stress and by blue light, and activated or restored by red light, thyroid, and progesterone. It's a copper enzyme, so it's likely to be damaged by excess iron. It is most active when it is associated with a mitochondrial lipid, cardiolipin, that contains saturated palmitic acid; the substitution of polyunsaturated fats lowers its activity. Mitochonrial function in general is poisoned by the unsaturated fats, especially arachidonic acid and DHA.

Creating a "deficiency" of DHA, even when an oil of known toxicity is used to replace the omega-3 oils, prevents retinal damage from light. Despite evidence of this sort, Mead Johnson is going ahead with the marketing of its baby formula containing added DHA which is indus-

trially extracted from algae. (Although the researchers who claim that DHA is beneficial haven't answered my letters, a representative of the company that manufactures it did answer my question about the actual composition of the oil, and acknowledged that they don't have any idea what the minor ingredients might be.)

When animals are made "deficient" in all the exogenous polyunsaturated fatty acids, linoleic and arachidonic acid as well as linolenic and DHA, they become remarkably resistant to all sorts of stress and toxins.

The polyunsaturated fats make the lungs more sensitive to excess oxygen or hyperventilation, they make the eyes more sensitive to light, and they make the brain more sensitive to fatigue.

The use of synthetic glucocorticoid hormone is standard in treating very premature babies, although it is known to contribute to eye damage. This is because it is considered necessary to improve the lung function of premature babies with respiratory distress. But there is no clear evidence that it is beneficial for lung function in the long run, and very clear evidence that it damages the brain and other organs. There is widespread agreement regarding the use of the glucocorticoids prenatally to accelerate lung development in women who seem likely to deliver prematurely. Natural cortisol is a factor that promotes lung development prenatally. But cortisol is also a signal produced by a stressed fetus, that triggers the birth process. Cortisol, or the synthetic glucocorticoid, inhibits progesterone production, and stimulates estrogen production, activating uterine contractions and other processes that terminate the pregnancy.

Apparently, it doesn't occur to many people that administering the glucocorticoid triggers premature birth, creating the problem they are intending to treat.

Recognizing causal connections between premature birth and respiratory distress and retinopathy of prematurity, it would be obvious that the greatest effort should be made to prevent the problems by improving the health of pregnant women. Hospitals, however, are invested in high technology systems for treating these problems, and even though their results are dismal, they can't make money by getting pregnant women to eat enough protein to prevent preeclampsia, which is a major cause of premature birth, or by treating the problems with salt, magnesium, progesterone, thyroid, and aspirin when the women haven't had a good diet.

Historically, preeclampsia has been blamed on the mother's or fetus's "bad genes," and that cultural bias was the setting in which these high technology prenatal and neonatal systems developed. High technology "neonatology" derives from the same ideology that motivated Josef Mengele's genetic research in Auschwitz. The idea of genetic determination is still motivating resistance to reasonable preventive approaches.

Thyroid, i.e., T_3, is very effective in accelerating lung development in the fetus, and it doesn't have any of the harmful effects of the synthetic glucocorticoids. It normalizes the hormones, increasing progesterone and decreasing estrogen, which are needed for full-term gestation, the opposite of the glucocorticoids' effects. While the cortisol-like drugs damage the brain and other organs, thyroid and progesterone protect them.

Old organisms, like newborns, are easily injured by all sorts of inappropriate excitation. As in premature babies, the aged eyes, lungs, and brain are especially sensitive to damage by stress. But all organs are subject to the same kinds of damage. Medical treatments for respiratory distress and macular degeneration in old people are often the same as those used so inappropriately for babies. The good health practices that can prevent the inflammatory and degenerative diseases can often make it possible for damaged tissues to recover, even in old age.

The pituitary hormones, especially prolactin and TSH, are proinflammatory, and darkness increases TSH along with prolactin, so to compensate for a light deficiency, the pituitary should be well-suppressed by adequate thyroid. Armour thyroid or Thyrolar or Cynoplus, Cytomel, would probably be helpful. (Eye-drops containing T_3 might be a way to restore metabolic activity more quickly.) Limiting water intake (or using salt generously) helps to inhibit prolactin secretion. The saturated fats protect against the body's stored PUFA, and keeping the blood sugar up keeps the stored fats from being mobilized. Aspirin (or indomethacin) is generally protective to the retina, analogously to its protection against sunburn. Adequate vitamin E is extremely important. There are several prescription drugs that protect against serotonin excess, but thyroid and gelatin (or glycine, as in magnesium glycinate) are protective against the serotonin and melatonin toxicities. Copper and magnesium deficiencies predispose to retinal damage. Red light is protective, blue light (or u.v.) is harmful, so wearing orange lenses would be helpful. Progesterone and pregnenolone, by reducing the stress reactions, should be helpful—in

the eye diseases of infancy and old age, as they are in the respiratory distress syndromes.

Altitude and Mortality

Ray Peat's Newsletter, 2006

THERE are some popular medical ideas that obstruct clear thinking about respiration. One is that high altitude deprives you of oxygen, and is likely to be bad for people with heart disease and cancer. Another is that breathing pure oxygen helps sick people to oxygenate their tissues while exerting less effort in breathing. These are both exactly wrong, and the errors have been explored in quite a few publications, but the ideas persist in the culture to such a degree that our perceptions and intuitions have been misled, making closely related things seem to be unrelated. In this culture, it is hard to see that heart disease, cancer, and cataracts all involve a crucial respiratory defect, with the production of too much lactic acid and too little carbon dioxide, which leads to a "swelling pathology": A pathological retention of water. The swollen heart beats poorly, the swollen lens turns milky, other cells divide rapidly as a result of swelling.

People who live at very high altitudes live significantly longer; they have a lower incidence of cancer[1] and heart disease,[2] and other degenerative conditions, than people who live near sea level. As I have written earlier, I think the lower energy transfer from cosmic radiation is likely to be a factor in their longevity, but several kinds of evidence indicate that it is the lower oxygen pressure itself that makes the biggest contribution to their longevity.

"Mountain sickness" is a potentially deadly condition that develops in some people when they ascend too rapidly to a high altitude. Edema of the lungs and brain can develop rapidly, leading to convulsions and death. The standard drug for preventing it is acetazolamide, which inhibits carbonic anhydrase and causes carbon dioxide to be retained, creating a slight tendency toward acidosis. This treatment probably mimics the retention of carbon dioxide that occurs naturally in altitude adapted people. The reasons for mountain sickness, and the reasons for the low incidence of heart disease, cancer, cataracts, etc., at high altitude, offer clues to the prevention of death and deterioration from many other causes.

When the weather in a particular place is cool, sunny and dry (which in itself is very good for the health) the atmospheric pressure usually is

higher than average. Although sunny dry weather is healthful, periods of higher pressure correspond to an increased incidence of death from heart disease and strokes.

The Haldane-Bohr effect describes the fact that oxygen and carbon dioxide destabilize each other's binding to hemoglobin. When oxygen pressure is high, the blood releases its carbon dioxide more easily. In stormy weather, or at high altitude, the lower oxygen pressure allows the body to retain more carbon dioxide. Carbon dioxide, produced in the cells, releases oxygen into the tissues, relaxes blood vessels, prevents edema, eliminates ammonia, and increases the efficiency of oxidative metabolism.

Hyperventilation, breathing excessively and causing too much carbon dioxide to be lost, is similar to being in the presence of too much oxygen; it's similar to being at low altitude with high atmospheric pressure, only worse. Therefore, the physiological events produced by hyperventilation can give us an insight into what happens when the atmospheric pressure is low, by looking at the events in reverse. Likewise, breathing 100 % oxygen has known harmful consequences, which are very similar to those produced by hyperventilation.

Hyperventilation is defined as breathing enough to produce respiratory alkalosis from the loss of carbon dioxide. Lactic acid is produced in response to the alkalosis of hyperventilation.

Breathing too much oxygen displaces too much carbon dioxide, provoking an increase in lactic acid; too much lactate displaces both oxygen and carbon dioxide. Lactate itself tends to suppress respiration.

Oxygen toxicity and hyperventilation create a systemic deficiency of carbon dioxide. It is this carbon dioxide deficiency that makes breathing more difficult in pure oxygen, that impairs the heart's ability to work, and that increases the resistance of blood vessels, impairing circulation and oxygen delivery to tissues. In conditions that permit greater carbon dioxide retention, circulation is improved and the heart works more effectively. Carbon dioxide inhibits the production of lactic acid, and lactic acid lowers carbon dioxide's concentration in a variety of ways.

When carbon dioxide production is low, because of hypothyroidism, there will usually be some lactate entering the blood even at rest, because adrenalin and noradrenalin are produced in large amounts to compensate for hypothyroidism, and the adrenergic stimulation, besides mobilizing glucose from the glycogen stores, stimulates the production

of lactate. The excess production of lactate displaces carbon dioxide from the blood, partly as a compensation for acidity. The increased impulse to breath ("ventilatory drive") produced by adrenalin makes the problem worse, and lactate can promote the adrenergic response, in a vicious circle.

Since the 1920s when A. V. Hill proposed that the prolonged increase in oxygen consumption after a short period of intense work, the "oxygen debt," was equivalent to the amount of lactic acid that had entered the circulation from the muscles' anaerobic work, and that it had to be disposed of by oxidative processes, physiology textbooks have given the impression that lactic acid accumulation was exactly the same as the oxygen debt. In reality, several things are involved, especially the elevation of temperature produced by the intense work. Increased temperature raises oxygen consumption independently of lactic acid, and lower temperature decreases oxygen consumption, even when lactic acid is present.

The idea of the "oxygen debt" produced by exercise or stress as being equivalent to the accumulation of lactic acid is far from accurate, but it's true that activity increases the need for oxygen, and also increases the tendency to accumulate lactic acid, which can then be disposed of over an extended time, with the consumption of oxygen. This relationship between work and lactic acidemia and oxygen deficit led to the term "lactate paradox" to describe the lower production of lactic acid during maximal work at high altitude when people are adapted to the altiude. Carbon dioxide, retained through the Haldane effect, accounts for the lactate paradox, by inhibiting cellular excitation and sustaining oxidative metabolism to consume lactate efficiently.

The loss of carbon dioxide from the lungs in the presence of high oxygen pressure, the shift toward alkalosis, by the Bohr-Haldane effect increases the blood's affinity for oxygen, and restricts its delivery to the tissues, but because of the abundance of oxygen in the lungs, the blood is almost competely saturated with oxygen.

At high altitude, the slight tendency toward carbon dioxide-retention acidosis decreases the blood's affinity for oxygen, making it more available to the tissues. It happens that lactic acid also affects the blood's oxygen affinity, though not as strongly as carbon dioxide. However, lactic acid doesn't vaporize as the blood passes through the lungs, so its effect on the lungs' ability to oxygenate the blood is the opposite of the

easily exchangeable carbon dioxide's. Besides dissociating oxygen from hemoglobin, lactate also displaces carbon dioxide from its (carbamino) binding sites on hemoglobin. If it does this in hemoglobin, it probably does it in many other places in the body.

According to Meerson, ascending more than 200 feet per day produces measurable stress. People seldom notice the effects of ascending a few thousand feet in a day, but it has been found that a large proportion of people have bleeding into the retina when they ascend to 10,000 feet without adequate adaptation. Presumably, similar symptomless bleeding occurs in other organs, but the retina can be easily inspected.

If hypothyroid people, with increased adrenalin and lactate, are hyperventilating even at rest and at sea level, when they go to a high altitude where less oxygen is available, and their absorption of oxygen is impaired by lactic acidemia, their "oxygen debt," conceived as circulating lactic acid, is easily increased, intensifying their already excessive "ventilatory drive," and in proportion to the lactic acid oxygen debt, oxygen absorption is further inhibited.

The lactic acid has to be disposed of, but their ability to extract oxygen is reduced. The poor oxygenation, and the increased lactic acid and free fatty acids cause blood vessels to become leaky, producing edema in the lungs and brain. This is very similar to the "multiple organ failure" that occurs in inflammatory conditions, bacteremia, congestive heart failure, cancer, and trauma.

Otto Warburg established that lactic acid production even in the presence of oxygen is a fundamental property of cancer. It is, to a great degree, the lactic acid which triggers the defensive reactions of the organism, leading to tissue wasting from excessive glucocorticoid hormone. The cancer's production of lactic acid creates the same kind of internal imbalance produced by hyperventilation, and if we look at the physiology of hyperventilation in the light of Warburg's description of cancer, hyperventilation imitates cancer metabolism, by producing lactic acid "even in the presence of oxygen." Lactate, a supposedly benign metabolite of the cancer cells, which appears in all the other degenerative conditions, including obesity, diabetes, Alzheimer's disease, multiple sclerosis, is itself a central factor in the degenerative process.

Working out the mechanisms involved in susceptibility to altitude sickness will clarify the issues involved in the things that cause most

people to die. At first, all of these changes occur in the regulatory systems, and so can be corrected.

The vitality of the mitochondria, their capacity for oxidative energy production, is influenced by nutrition and hormones. In healthy people, mitochondria work efficiently at almost any altitude, but people with damaged or poorly regulated mitochondria are extremely susceptible to stress and hyperventilation. Progesterone, testosterone, and thyroid (T_3 and T_2) are protective of normal mitochondrial function, by both local and systemic effects.

The changes that occur in malnutrition and hypothyroidism affect the mitochondria in a multitude of ways, besides the local effects of the thyroid and progesterone deficiency.

Increased estrogen, nitric oxide, excitatory amino acids, cortisol, lactate, free unsaturated fatty acids, prolactin, growth hormone, histamine, serotonin, tumor necrosis factor and other pro-inflammatory cytokines and kinins, and a variety of prostaglandins and eicosanoids, have been identified as anti-mitochondrial, anti-respiratory agents. Edema itself can be counted among these agents. (Carbon dioxide itself directly reduces tissue edema, as can be seen in studies of the cornea.) Thyroid, progesterone, magnesium, glucose, and saturated fatty acids are among the central protective elements.

The similarity of the changes occurring under the influence of estrogen excess, oxygen deprivation, aging, and ionizing radiation are remarkable. People who think that radiation's biological effects are mainly on the DNA, and that estrogen acts through "estrogen receptors," aren't interested in the parallels, but the idea of a common respiratory defect, activating common pathways, suggests that there is something useful in the perception that irradiation, hypoxia, and aging have estrogenic effects.

Irradiation by ultraviolet, gamma, or x-rays, and even by blue light, is damaging to mitochondrial respiration. All of the ionizing radiations produce immediate and lingering edema, which continues to damage metabolism in a more or less permanent way, apart from any detectable mutagenic actions. The amount of water taken up following irradiation can be 20 % to 30 % of the normal weight, which is similar to the amount of swelling that intense work produces in a muscle, and to the weight increase under hormonal imbalances. The energy changes produced by irradiation in, for example, the heart, appear to accelerate the changes

produced by aging. Since unsaturated fats accumulate in the respiratory system with aging, and are targets for radiation damage, the involvement of these fats in all sorts of antirespiratory degenerative processes deserves more attention. Darkness, like irradiation, excess lactate, and unsaturated fats, has the diabetes-like effect of greatly reducing the ability of muscle to absorb sugar, while light stimulates respiration.

When the ideas of "stress," "respiratory defect," and "hyperventilation" are considered together, they seem practically interchangeable.

The presence of lactic acid, which indicates stress or defective respiration, interferes with energy metabolism in ways that tend to be self-promoting. Harry Rubin's experiments demonstrated that cells become cancerous before genetic changes appear. The mere presence of lactic acid can make cells more susceptible to the transformation into cancer cells.[3] The implications of this for the increased susceptibility to cancer during stress, and for the increased resistance to cancer at high altitude, are obvious.

Blocking the production of lactic acid can make cells more resistant;[4] if lactic acid were merely a useful fuel, it's hard to see how poisoning its formation could improve cell survival. But it happens to be an energy-disruptive fuel, interfering with carbon dioxide metabolism, among other things.

Hyperventilation is present in hypothyroidism, and is driven by adrenalin, lactate, and free fatty acids. Free fatty acids and lactate impair glucose use, and promote edema, especially in the lungs. Edema in the lungs limits oxygen absorption. Swelling of the brain, resulting from increased vascular permeability and the entry of free fatty acids, reduces its circulation and oxygenation; lactic acidemia causes swelling of glial cells. Swelling of the endothelium increases vascular resistance by making the channel narrower, eventually affecting all organs. Cells of the immune system release tumor necrosis factor and other inflammatory cytokines, and the bowel becomes more permeable, allowing endotoxin and even bacteria to enter the blood. Endotoxin impairs mitochondria, increases estrogen levels, causes Kupffer cells in the liver to produce more tumor necrosis factor, etc. Despite its name, tumor necrosis factor stimulates the growth and metastasis of some types of cancer. Dilution of the body fluids, which occurs in hypothyroidsim, hyperestrogenism, etc., stimulates tumor growth.

The inflammatory factors that can promote cell growth can, with just slight variation, deplete cellular energy to the extent that the cells die from the energetic cost of the repair process, or mutate from defective repairs. Niacinamide can have an "antiinflammatory" function, preventing death from multiple organ failure, by interupting the reactions to nitric oxide and peroxynitrile.[5] The cells' type, environment, and history determine the different outcomes.

Cataracts, cancer, congestive heart failure, seemingly such different degenerative problems, have the same sort of metabolic problem, leading to the abnormal absorption of water by cells, disrupting their normal functions.

The same simple metabolic therapies, such as thyroid, progesterone, magnesium, and carbon dioxide, are appropriate for a great range of seemingly different diseases. Other biochemicals, such as adenosine and niacinamide, have more specific protective effects, farther downstream in the "cascade" effects of stress.

There are many little cliches in the medical culture that prevent serious thought about integral therapy: "Progesterone is the pregnancy hormone," "thyroid makes your heart work too hard," "thyroid uncouples mitochondrial phosphorylation," "magnesium has nothing to do with thyroid or progesterone," "lactate provides energy," etc. But many of these minor cliches are held in place by deep theoretical errors about the nature of cells and organisms. Once those have been corrected, there should be progress toward more powerful integral therapies.

Aspirin, Brain, and Cancer

Ray Peat's Newsletter, 2006

WHEN a drug such as caffeine or aspirin turns out to have a great variety of protective effects, it's important to understand what it's doing.

Because aspirin has been abused by pharmaceutical companies that have competing products to sell, as well as by the original efforts to promote aspirin itself, people can easily find reasons why they shouldn't take it.

Early in the 20th century, people were told that fevers were very bad, and that aspirin should be used whenever there is a fever.

In the 1980s, there was a big publicity campaign warning parents that giving aspirin to a child with the flu could cause the potentially deadly Reye syndrome. Aspirin sales declined sharply, as sales of acetaminophen (Tylenol, etc.) increased tremendously. But in Australia, a study of Reye syndrome cases found that six times as many of them had been using acetaminophen as had used aspirin.[1]

Until the 1950s and 1960s, when new products were being promoted, little was said about the possibility of stomach ulceration from aspirin. Lately, there has been more publicity about the damage it can do to the stomach and intestine, much of it in connection with the sale of the new "COX-2 inhibitors." (These new drugs, rather than protecting the circulatory system as aspirin does, damage it.) Aspirin rapidly breaks down into acetic acid and salicylic acid (which is found in many fruits), and salicylic acid is protective to the stomach and intestine, and other organs. When aspirin was compared with the other common antiinflammatory drugs, it was found that the salicylic acid it releases protects against the damage done by another drug.[2,3] Repeated use of aspirin protects the stomach against very strong irritants. The experiments in which aspirin produces stomach ulcers are designed to produce ulcers, not to realistically model the way aspirin is used.

Recently, the public has been led to believe that drugs are being designed to fit certain cellular "receptors." The history of the "COX-2 inhibitors" is instructive, in a perverse way. The structures of DES and other synthetic estrogens were said to relate to "the estrogen receptor." Making these estrogenic molecules more soluble in water made them

somewhat anti-estrogenic, leading to products such as Tamoxifen. But some of the molecules in this group were found to be antiinflammatory. The structure of Celecoxib and other "COX-2 inhibitors" is remarkably similar to the "designer estrogens." Considering this, it's a little odd that so few in the U.S. are openly discussing the possibility that estrogen's function is directly related to inflammation, and involves the production of many inflammatory mediators, including COX-2.[4–8]

Soot and smoke contain many chemicals that produce inflammation.[9] In the 1930s, soot was known to be both carcinogenic and estrogenic, and analysis of its components led to the production of the early commercial estrogens. Any intelligent person reading the chemical and biological publications of that time will see how closely associated cancer, inflammation, and estrogen are.

Soon after vitamin E was discovered, tocopherol was defined as a brain-protective, pregnancy protective, male fertility protective, antithrombotic, antiestrogenic agent. But very soon, the estrogen industry made it impossible to present ideas that explained vitamin E, progesterone, vitamin A, or thyroid hormone in terms of the protection they provide against estrogenic substances. Since the polyunsaturated fats caused the same conditions that were caused by unopposed estrogen, vitamin E came to be known as an "antioxidant," because it reduced their toxicity. (Vitamin E is now known to suppress COX-2, synergizing with aspirin and opposing estrogen.)

In 1970, when I was beginning to see the ways in which unopposed estrogen and accumulated polyunsaturated fats interacted with a vitamin E deficiency during aging and in infertility, I got some prostaglandins to experiment with, since they are products of the oxidation of linoleic acid. The prostaglandins are an interesting link between estrogens and inflammation, in normal physiology as well as in disease.

I wanted to test their effects on the uterus, especially the sites where the embryos implant. There was a theory that the electrical charge of the surface of the uterus was decreased at the implantation sites, to reduce the repulsion between two negatively charged things. Although there were regions of lower surface charge along the lining of the uterus, the charge changed as waves of muscle contraction moved along the uterus, and the prostaglandins affected the contractions.

To understand the differences between the different types of prostaglandin, I tested them on my arm, and those with the most hy-

droxyl groups produced regions with an increased negative charge. For comparison, I exposed another spot to sunlight for an hour, and found that there was a similar increase in the negative charge in that spot. Apparently the prostaglandins were causing an injury or excitation, a mild inflammation, in the skin cells.

A few years later, aspirin was found to inactivate the enzyme that forms prostaglandins, by the transfer of the acetyl radical to the enzyme. This became the orthodox "explanation" for what aspirin does, though it neglected to explain that salicylic acid (lacking the acetyl radical) had been widely known in the previous century for its very useful antiinflammatory actions. The new theory did explain (at least to the satisfaction of editors of medical magazines) one of aspirin's effects, but it distracted attention from all the other effects of aspirin and salicylic acid.

Aspirin is an antioxidant that protects against lipid peroxidation, but it also stimulates mitochondrial respiration. It can inhibit abnormal cell division, but promote normal cell division. It can facilitate learning, while preventing excitotoxic nerve injury. It reduces clotting, but it can decrease excessive menstrual bleeding. These, and many other strangely beneficial effects of aspirin, strongly suggest that it is acting on very basic biological processes, in a coherent way.

In explaining aspirin's effects, as in explaining those of estrogen and progesterone, or polyunsaturated fats and vitamin E, I think we need concepts of a very broad sort, such as "stability and instability."

The COX (cyclooxygenase) enzymes, that make prostaglandins, are just one system among many that are activated by stress. Aromatase, that makes estrogen, enzymes that make histamine, serotonin and nitric oxide, the cytokines, and the stress-induced hormones of the pituitary and adrenal glands, are turned on in difficult situations, and have to be turned off when the threat has been overcome. The production of energy is the basis for overcoming all threats, and it has to be conserved in readiness for future needs.

The fetus produces saturated fats such as palmitic acid, and the monounsaturated fat, oleic acid, which can be turned into the Mead acid, ETrA (5,8,11-eicosatrienoic acid), and its derivatives, which are antiinflammatory, and some of which act on the "bliss receptor," or the cannibinoid receptor. In the adult, tissues such as cartilage, which are protected by their structure or composition from the entry of exogenous

fats, contain the Mead acid despite the presence of linoleic acid in the blood.

At birth, the baby's mitochondria contain a phospholipid, cardiolipin, containing palmitic acid, but as the baby eats foods containing polyunsaturated fatty acids, the palmitic acid in cardiolipin is replaced by the unsaturated fats. As the cardiolipin becomes more unsaturated, it becomes less stable, and less able to support the activity of the crucial respiratory enzyme, cytochrome oxidase.

The respiratory activity of the mitochondria declines as the polyunsaturated oils replace palmitic acid, and this change corresponds to the life-long decline of the person's metabolic rate.

In old age, a person's life expectancy strongly depends on the amount of oxygen that can be used. When the mitochondria can't use oxygen vigorously, cells must depend on inefficient glycolysis for their energy.

Estrogen activates the glycolytic pathway, while interfering with mitochondrial respiration. This resembles the aged or stressed metabolism, in which lactic acid is produced instead of carbon dioxide.

Aspirin activates both glycolysis and mitochondrial respiration, and this means that it shifts the mitochondria away from the oxidation of fats, toward the oxidation of glucose, resulting in the increased production of carbon dioxide. Its action on the glycolytic enzyme, GAPDH, is the opposite of estrogen's.

The shift away from fat oxidation under the influence of aspirin doesn't lead to an accumulation of free fatty acids in the circulation, since aspirin inhibits the release of fatty acids from both phospholipids and triglycerides. Estrogen has the opposite effects, increasing fat oxidation while increasing the level of circulating free fatty acids, since it activates lipolysis, as do several other stress-related hormones.

The polyunsaturated fatty acids, such as linolenic, linoleic, arachidonic, EPA, and DHA, have many directly toxic, antirespiratory actions, apart from the production of the prostaglandins or eicosanoids. Just by preventing the release of these fatty acids, aspirin would have broadly antiinflammatory effects.

Since the polyunsaturated fats and prostaglandins stimulate the expression of aromatase, the enzyme that synthesizes estrogen, aspirin decreases the production of estrogen. So many of aspirin's effects oppose those of estrogen, it would be tempting to suggest that its "basic action" is the suppression of estrogen. But I think it's more likely that both estrogen

and aspirin are acting on some basic processes, in approximately opposite ways.

Bioelectrical functions, and the opposition between carbon dioxide and lactic acid, and the way water is handled in cells, are basic conditions that have a general or global effect on all of the other more specific biochemical and physiological processes. Originally, estrogen and progesterone were each thought to affect only one or a few biochemical events, but it has turned out that each has a multitude of different biochemical actions, which are integrated in globally meaningful ways. The salicylic acid molecule is much smaller and simpler than progesterone, but the range of its beneficial effects is similar. Because of aspirin's medical antiquity, there has been no inclination to explain its actions in terms of an "aspirin receptor," as for valium and the opiates, leaving its biochemistry, except for the inadequate idea of COX-inhibition, simply unexplained.

If we didn't eat linoleic acid and the other so-called "essential fatty acids," we would produce large amounts of the "Mead acid," n-9 eicosatrienoic acid, and its derivatives. This acid in itself is antiinflammatory, and its derivatives have a variety of antistress actions. The universal toxicity of the polyunsaturated fats that suppress the Mead fats as they accumulate, and the remarkable vitality of the animals that live on a diet deficient in the essential fatty acids, indicate that the Mead fats are important factors in the stability of our mammalian tissues. This protective lipid system probably interacts with cellular proteins, modifying the way they bind water and carbon dioxide and ions, affecting their electrons and their chemical reactivity.

If salicylic acid and the structurally similar antiinflammatories, local anesthetics, muscle relaxants, expectorants, and antihistamines, act as surrogates for the absent Mead acid family, and thereby act as defenses against all the toxic effects of the unstable fats, it would explain the breadth and apparent coherence of their usefulness. And at the same time it explains some of the ways that estrogen goes out of control, when it exacerbates the toxicity of the accumulated unstable fats.

The competition between aspirin and salicylic acid, and other antiinflammatories, for the active site on the COX enzyme,[10] shows that the structural features of these molecules are in some ways analogous to those of the polyunsaturated fatty acids. Wherever there are phospholipids, free fatty acids, fatty acid esters, ethers, etc. (i.e., in mitochondria,

chromosomes, cytoskeleton, collagen networks—essentially everywhere in and around the cell), the regulatory influence of specific fatty acids—or their surrogates—will be felt.

Although it would undoubtedly be best to grow up eating foods with relatively saturated fats, the use of aspirin preventively and therapeutically seems very reasonable under the present circumstances, in which, for example, clean and well ripened fruits are not generally available in abundance. Preventing blindness, degenerative brain diseases, heart and lung diseases, and cancer with aspirin should get as much support as the crazy public health recommendations are now getting from government and foundations and the medical businesses.

When people with cancer ask for my recommendations, they usually think I'm joking when I tell them to use aspirin, and very often they don't take it, on the basis of what seems to be a very strong cultural prejudice. Several years ago, a woman whose doctors said it would be impossible to operate on her extremely painful "inflammatory breast cancer," had overnight complete relief of the pain and swelling from taking a few aspirins. The recognized anti-metastatic effect of aspirin, and its ability to inhibit the development of new blood vessels that would support the tumor's growth, make it an appropriate drug to use for pain control, even if it doesn't shrink the tumor. In studies of many kinds of tumor, though, it does cause regression, or at least slows tumor growth. And it protects against many of the systemic consequences of cancer, including wasting (cachexia), immunosuppression, and strokes.

Opiates are the standard medical prescription for pain control in cancer, but they are usually prescribed in inadequate quantities, "to prevent addiction." Biologically, they are the most inappropriate means of pain control, since they increase the release of histamine, which synergizes with the tumor-derived factors to suppress immunity and stimulate tumor growth.

It has recently become standard practice in most places to advise a person who is having a heart attack to immediately chew and swallow an aspirin tablet.

The same better-late-than-never philosophy can be applied to Alzheimer's disease, Parkinson's disease, and other degenerative nerve diseases. Aspirin protects against several kinds of toxicity, including excitotoxicity (glutamate), dopamine toxicity, and oxidative free radical toxicity. Since its effects on the mitochondria are similar to those of

thyroid (T_3), using both of them might improve brain energy production more than just thyroid. (By activating T_3, aspirin can sometimes increase the temperature and pulse rate.) Magnesium, niacinamide, and other nerve protective substances work together.

In multiple organ failure, which can be caused by profound shock caused by trauma, infection, or other stress, aspirin is often helpful, but carbon dioxide and hypertonic glucose and sodium are more important.

Aspirin, like progesterone or vitamin E, can improve fertility, by suppressing a prostaglandin, and improving uterine circulation.

Although the animal studies that showed stomach damage from aspirin often used single doses equivalent to 10 or 100 aspirin tablets, the slight irritation produced by a normal dose of aspirin can be minimized by dissolving the aspirin in water. The stomach develops a tolerance for aspirin over a period of a few days, allowing the dose to be increased if necessary. And both aspirin and salicylic acid can be absorbed through the skin, so rheumatic problems have been treated by adding the drug to bath water.

The unsaturated (n-6 and n-3) fats that accumulate in our tissues, instead of being part of the system for reestablishing order and stability, tend to amplify the instability that is triggered by excitation, by estrogen, or by external stresses.

I think it's important that we don't allow the drug publicists to obscure the broad importance of substances such as aspirin, vitamin E, progesterone, and thyroid. For 60 years, a myth that was created to sell estrogen has harmed both science and the health of many people.

Autonomic Systems

Ray Peat's Newsletter, 2006

PEOPLE like Walter Cannon and Wilhelm Reich popularized the idea of the autonomic nervous system, but they were just systematizing ideas that had been developing since the beginning of the century. Their views were the context in which Selye's idea of stress developed.

The anatomical components of the nervous system that were called the sympathetic ("fight or flight," adrenergic) system and the parasympathetic ("vegetative") system are still important factors in physiological thinking, and despite the great complexity that has grown up around them, there is still a tendency to identify the systems with polarities of mood or emotion. The idea of polarities is useful, but it easily leads to error.

(The sympathetic system includes a chain of ganglia along the spine, and its functions include dilating the pupils and accelerating the heart. The parasympathetic system is also called the cranio-sacral system, from the location of its ganglia, and among its functions are slowing the heart and constricting the pupils. However, despite several decades of research, the actions of "sympathetic" and "parasympathetic" nerves in most organs aren't understood.)

If the "adrenaline side" of the nervous system is responsible for the reactions to pain and threat, reactions of fear and rage, then the opposite side tends to be given attributes such as peace and pleasure, and the fact that these oppositions are often true has led to a climate in which the adrenergic reactions are seen as "bad," and the opposite reactions as "good." When adrenalin was identified as an agent of the sympathetic nervous system, there was a search for the "opposing" agent of the parasympathetic system. Histamine was an early candidate, before acetylcholine was discovered to be the main parasympathetic agent. This view of histamine was fostered by the older idea of "trophic nerves," which easily became identified with the parasympathetic system. When acetylcholine was identified as the transmitter or agent of the parasympathetic system, it tended to take on many of the qualities, including the "trophic" functions, that had grown up around the idea of the parasympathetic system, but the emphasis on acetylcholine led to a general neglect of the associations of histamine, and the mast cells that

produce much of it, with the autonomic nervous system. (The current trend seems to be emphasizing a close integration of mast cell function with nervous function.) Nitric oxide has recently been identified as another parasympathetic "transmitter." Nitric oxide and histamine are both very important factors in degenerative inflammatory diseases, but their association with the parasympathetic nervous system has given them an aura of benevolence.

I think it's useful to compare the autonomic nervous system with the pituitary, not just because some of the pituitary hormones are called "trophic" hormones (e.g., luteotrophic, adrenocorticotrophic), but because their important adaptive functions can themselves be the cause of serious problems. An excess of the thyroid stimulating hormone, for example, causes degeneration and cancer development in the thyroid gland, and animals deprived of their pituitary gland, but given thyroid, live longer than intact animals.

If slaves are starved and beaten frequently, they aren't very productive, they don't live long, and they might rebel. Workers that are healthy and working for a common goal that they understand are more productive. Cells that are well energized perform their functions with minimal cues, but deprived cells that have to be forced to function are likely to die unexpectedly, or to reproduce inappropriately, or to change their identity.

Professors often make a strong impression on their students, but, especially in technical or scientific fields, they usually do this by controlling the discourse, so that radical questioning is excluded. What they don't know "isn't knowledge." Under the pressure of "getting a professional education," students appreciate organizing principles and mnemonic devices, but this gives traditional ways of systematizing knowledge tremendous power that, in practice, is far more important than mere experimental results. (Experiments that don't acknowledge the ruling metaphors are almost universally considered inadmissable, unpublishable.)

Some obvious questions about the autonomic system have been commonly ignored or minimized by physiologists. If "stress" is the stimulus that causes the sympathetic system to increase its activity, what is the stimulus for increased activity of the parasympathetic system? What accounts for the relative balance between the two sides of the system, or their imbalance? The fact that the answers aren't obvious has left

the questions largely to psychiatrists and psychologists. Wilhelm Reich, who tried to provide answers in terms of developmental interactions between the organism and its environment, found that the question led him to investigate psychosomatic disease, sexual repression, cancer, and fascism, with disastrous results for himself.

Chinese medicine was familiar with many of the functions of the autonomic nervous system at a time when western medicine was organized around "the humors." It's easy for contemporary "western" people to see that the "winds" and the hot and cold principles of Chinese tradition are metaphors, but they are reluctant to see that their own system has grown up within very similar traditional metaphoric polarities.

The successes of even a good metaphor can cause people to neglect details that could support a more complete and accurate image of reality.

Contemporary science carries a load of bad metaphors, because the educational system doesn't tolerate a critical attitude. Potentially, a good metaphor (e.g., Vernadsky's suggestion that an organism is "a whirlwind of atoms") could blow away many bad metaphors, but the present organization of science is tending in the other direction: Commercial interests are creating a culture in which their metaphors are replacing the traditional science in which there was a certain amount of honest intellectual exploration.

In talking about consciousness, sleep, stress, biological rhythms, aging, and energy, I have often focussed on the efficient use of oxygen for energy production by the mitochondria, i.e., cellular respiration. Every situation demands a special kind of adaptation, and each kind of adaptation requires a special distribution of cellular and organic activity, with its supporting local respiratory activity.

There is a lot of local self-regulation in the adapting organism, for example when the activated tissue produces increased amounts of carbon dioxide, which dilates blood vessels, delivering more oxygen and nutrients to the tissue. But the distribution of excitation, and the harmonious balancing of the organism's resources and activities, is achieved by the actions of the cortex of the brain, acting on the subordinate nerve nets, adjusting many factors relating to energy production and use.

On the level of the mitochondria, adrenaline and acetylcholine have slightly different effects. (Metabolic studies with isolated mitochondria are so remote from the normal cellular condition that their results are nothing more than a hint of what might be occurring in the cell.) Acetyl-

choline appears to shift the proportion of the fuels used (increasing the oxidation of alpha-ketoglutarate, with the production of carbon dioxide) and increasing the efficiency of energy conservation (phosphorylation, producing ATP) so that less oxygen is needed, while adrenaline increases the rate of oxygen consumption (and succinate oxidation). This would be consistent with F. Z. Meerson's conception of the parasympathetic function as one of the "stress limiting" systems.

On the level of the whole cell, organ, and organism, the parasympathetic function limits oxygen consumption in a variety of ways, including the reduction of blood flow. Acetylcholine, like histamine and serotonin, activates glycolysis, the conversion of glucose to lactic acid, which provides energy in the absence of oxygen.

The effects of a little adrenaline, and a lot of adrenaline, are very different, with a high concentration of adrenaline decreasing the efficiency of phosphorylation. In the stressed heart, this effect of excess adrenaline can be fatal, especially when it is combined with adrenaline's acceleration of clotting, liberation of fatty acids, and frequently of calcium, and constriction of blood vessels.

Seventy years ago, autonomic control of blood vessels seemed to be a matter of nerve fibers that constrict them, and other fibers that cause them to dilate, but that idea hasn't worked for a long time.

Ever since I noticed that the students in our physiology lab who tried to use adrenaline to revive their rats weren't successful, I have wondered about the television shows in which adrenaline is given to patients with heart problems. Under some conditions adrenaline does increase circulation to the heart, but extreme stress doesn't seem to be among those conditions.

Too much serotonin, histamine, acetylcholine, and polyunsaturated fatty acids, like too much adrenalin, can cause spasms of the coronary arteries, along with disturbances of mitochondrial respiration. In stress, these substances are almost sure to be present in excess. (Anti-serotonin drugs are effective for a variety of heart problems, and other degenerative diseases.)

By increasing the production of lactic acid and the loss of carbon dioxide, exaggerated nervous stimulation (especially the excess of acetylcholine, histamine, and serotonin) can cause a variety of problems, including generalized vasoconstriction and systemic alkalosis, as well as increased intracellular alkalinity. This metabolic pattern is characteristic

of many kinds of stress, including cancer. (Elsewhere, I have referred to this pattern as "relative hyperventilation.") The metabolic effects probably account for some of the "paradoxical" effects of the autonomic agents.

When nutrition and thyroid function, light, atmospheric pressure, and other conditions are favorable, the autonomic transmitters (e.g., acetylcholine, histamine, serotonin, adrenalin) and pituitary hormones and other "signal substances" are kept within safe limits.

Because the substances released from various cells under the influence of the autonomic nerves (histamine and serotonin, for example) stimulate cell division, injuries which produce clots and vascular spasms will also stimulate the formation of new blood vessels, a process that is essential for the adaptation of tissues to prolonged stress.

These stress-induced agents are appropriately included in the "vegetative" (parasympathetic) nervous system, because they promote vegetation, i.e., the proliferation of substance.

Adrenaline, and the sympathetic nerves, have the opposite function, of restraining cell division, and they also oppose the pro-inflammatory functions of those parasympathetic agents.

Estrogen tends to shift autonomic balance toward the parasympathetic side, away from the sympathetic/adrenergic. Recalling that stress, hypothyroidism, and aging increase the activity of aromatase in various tissues, with local production of estrogen, and that tissue-bound estrogen stays at a high level in postmenopausal women despite the lower level of estrogen in the serum, it's worthwhile looking at the effects of estrogen on the various components of the so-called autonomic nervous system.

One injection of estrogen can induce a large increase in the number of sympathetic nerves in the ovaries. At menopause, a similar "invasion" of sympathetic nerves occurs. The polycystic ovary (which is even more common after menopause than before, and some studies have found the condition in 20 % of premenopausal women) responds to estrogen by producing nerve growth factor(s), and growing a large number of new sympathetic nerves. Although the hyperestrogenism associated with the polycystic ovary syndrome has many harmful effects, the invasion of the ovary by adrenergic nerves apparently protects it from the development of cancer.

Parasympathetic nerves, pituitary hormones and mast cells activate the ovaries. The number of mast cells in the ovaries is increased by

the pituitary hormones (including the thyroid stimulating hormone), and by estrogen.[1] Estrogen is the most potent of these hormones in causing the cells to release histamine. The overgrowth of the sympathetic nerves in the polycystic ovary causes the number and activity of mast cells to decrease, possibly as a protective adaptation against excessive stimulation from the many pro-inflammatory factors. The mast cells are needed for the follicles to rupture, so their suppression prevents ovulation.

The nervous system is closely involved in controlling the growth of tissues, and it has been argued (R.E. Kavetsky reviewed the subject in his book, emphasizing the role of depression in development of cancer) that cancer results from reduced activity of the sympathetic nerves, or unopposed action of the parasympathetic system. That stress has a role in cancer is acknowledged by the scientific establishment, but the nervous system's direct involvement in the regulation of cellular metabolism, cell division, and other processes that are central to the cancerous state is either flatly denied or simply ignored.

Although mast cells have been known to be a common component of tumors for many years, it is only recently that antihistamines and other antiinflammatory drugs have been recognized as valuable therapies in cancer. The whole issue of the role of nerves in tumor development and physiology has been submerged by the mystique of the "intrinsically bad cancer cell."

In Alzheimer's disease, there has been a great investment in the doctrine that drugs to promote the function of cholinergic (acetylcholine forming) nerves will restore lost mental function, or at least retard the progression of the disease. The success of anticholinergic drugs in treating several degenerative brain diseases is probably embarrassing to the companies whose cholinergic-intensifying drugs aren't very successful. Conveniently for them, these formerly "anticholinergic" drugs are now being called anti-excitotoxic or anti-glutamatergic drugs. There is no serious conflict in the terminology, since the cholinergic processes (like the serotonergic processes) are closely associated with excitotoxic nerve damage. The cholinergic drugs will probably be sold as long as their patents are effective, and then will be quietly forgotten.

The modern conception of pharmacology, with receptors and transmitters turning functions on or off, has turned into an unproductive and dangerous scholasticism. No one will ever successfully count the

number of transmitter angels dancing on the variable sites of the variable receptor molecules. The functional "meaning" of a receptor or transmitter changes according to circumstances, and the effect of activating a particular nerve depends on surrounding conditions, and on preceding conditions. Each cell integrates stimuli adaptively.

If no reflex is simply mechanical and innate, then all reflexes are conditional. (M. Merleau-Ponty argued against the validity of the reflex concept itself, because of this conditionality.) P. K. Anokhin's concept of the "Acceptor of Action" (described in my book, Mind and Tissue) provides an image in which we can see the "set-points" for the relatively "autonomic" reflexes as reflections of the general needs of the organism. The local tissue reflexes, the organ reflexes, the spinal reflexes, etc., are variable, according to their energetic resources, and according to the way in which they are organized under the influence of the cerebral cortex and the environment.

The reality is more complex than the philosophy of the drug industry imagines, but the solutions of problems can be much simpler, if we think in terms of energetic support, rather than the over-concretized interventions of the pharmacologists. In hypothyroidism, it is common for there to be an excess of adrenalin/noradrenalin, serotonin, histamine, and some of the pituitary hormones. Correcting thyroid function can immediately correct many problems, but especially when the energy deficiency has caused anatomical adjustments (redistribution of blood vessels and mast cells, for example) it's important to make the environment supportive in as many ways as possible.

In polycystic ovaries, menopausal symptoms, arthritis, angina pectoris, multiple sclerosis, some kinds of dementia, migraine, and emphysema, the relief achieved with a simple improvement of cellular energy can be rapid and complete. Presumably a similar process of biological reorganization is involved in the occasional spontaneous regression of tumors.

Although I don't think the autonomic nervous system, with its sympathetic and parasympathetic divisions, exists in the way it has traditionally been conceived, the idea can be useful if we think of using drugs and other factors in ways that tend to "quiet an overactive autonomic nervous system."

BSE, Mad Cow, Scrapie, etc.

Stimulated Amyloid Degeneration and the Toxic Fats

Ray Peat's Newsletter, 2007

I have written before about the protective effects of carbon dioxide and progesterone, especially for the brain, and how the structure of cell water is affected by adsorbed and dissolved materials, and by metabolic energy. In the high energy (rested) state, cell water behaves as if it were colder than its real temperature, and this affects the behavior of proteins and fats in the cell, allowing "oily" surfaces to remain in contact with the more orderly water. Carbon dioxide spontaneously combines with the amino groups in proteins, stabilizing the normal functional conformation. The loss of carbon dioxide affects the structure of all proteins in the body, and the loss of cellular energy affects the structure of the intracellular proteins and their associated molecules.

In scrapie and many other degenerative diseases (the amyloidoses), proteins condense into fibrils that tend to keep enlarging, with a variety of very harmful effects. The condensation of the "amyloid" proteins is sensitive to temperature, and a slight increase in the disorder of the water can induce functional proteins to change their conformation so that they spontaneously associate into fibrous masses. In the absence of sufficient carbon dioxide, all proteins are susceptible to structural alteration by the addition of sugars and fats and aldehydes, especially under conditions that favor lipid peroxidation.

The amyloidoses affect different tissues in different ways, but when they occur in the brain, they produce progressive loss of function, with the type of protein forming the fibrils determining the nature of the functional loss. The protein which carries thyroid hormone and vitamin A, transthyretin, can produce nerve and brain amyloid disease, but it can also protect against other amyloid brain diseases; in Alzheimer's disease, Parkinson's disease, Huntington's disease, and the "prion diseases" (scrapie, kuru, CJD, BSE, etc.) amyloid particles are formed by different proteins. The transthyretin protein which is binding small molecules resists condensation into the amyloid fibrils, but without its normal vitamin A and thyroid hormone, it can create toxic fibrils.[1]

Around 1970 I read E. J. Field's suggestion that aging tissues and tissues affected by viral diseases showed some similar structures ("in-

clusion bodies") under the electron microscope. In following up those observations, it turned out that old tissues appeared to develop antigens "identical with, or similar to," scrapie-infected young tissues. The premature aging caused by removal of the thymus gland in newborn animals produced similar results.

Field's group and others (e.g., Alpers) were clearly showing that the scrapie infection involved proteins, but not viruses with nucleic acids. In one of Field's last publications (1978), he even suggested that the infectious process might depend on a structural rearrangement of the host's molecules, similar to the idea which is now known as the "prion hypothesis." Field's suggestion was an important advance in the theory of aging, and the evidence supporting it is now voluminous, but that work has been omitted from the official histories.

Although phenomena of "imprinting" and non-genetic inheritance had been established earlier, the dogmatism of genetics led the scientific establishment to reject everything that challenged the primacy of DNA. When I mentioned to my professors (in 1971) the evidence that scrapie was transmitted without nucleic acid, I could see from their reactions that it would be a very long time before much progress would be made in understanding the degenerative brain diseases. When the exact structure of the "infectious" protein was later worked out, and the 1997 Nobel Prize awarded (to Stanley Prusiner), I was surprised that no one from Field's group was included. (In 1976, a Nobel Prize had been awarded to D.C. Gajdusek, for his promotion of the idea of "slow viruses" in general, and particularly for arguing that scrapie, CJD and kuru were caused by slow viruses.)

In reading Prusiner's autobiographical statements, I was even more surprised to see that he claimed to have been puzzled to find out, around 1983, that the infectious agent was a protein. I had thought that my professors were lethargic authoritarians when they refused to look at the evidence in 1970–72, but Prusiner's expression of puzzlement so many years later over the absence of nucleic acid in the infectious agent is hard to account for.

In my own research in 1971, I was interested in another kind of age-related "inclusion body," which was variously called lipofuscin, age pigment, and ceroid pigment. This brown (yellow autofluorescent) pigment contained proteins and metals, as well as polyunsaturated lipids, and overlapped in many ways with the amyloid bodies. All

of these inclusion bodies were known to be associated with radiation injury, aging, and hormonal-nutritional imbalances. Excess of estrogen, polyunsaturated fatty acids, and oxidative metals were major factors in the development of lipofuscin, and estrogen was also known to cause other types of "inclusion bodies" to develop in cells.

Although very little was known about the composition of the inclusion bodies (they were usually thought to be organelles damaged by free radical activity, or antibodies resulting from autoimmunity), their involvement in aging and degenerative disease was clear, and it was widely known that ionizing radiation accelerated their formation. But it was just at this time that the national research priorities of the U.S. were redirected toward genetic explanations for all major diseases, with for example the "war on cancer" centering on the concepts of the "oncogene" and the cancer virus. Since the "slow virus" of cancer, or the viral oncogene, requires activation by something in the environment, its function is to distract the public's attention from those environmental causes of disease, viz., radiation and chemical pollution.

The U.S. Public Health Service has historically been one of the branches of the military, and currently has 6000 commissioned officers. It has been intimately involved in all aspects of chemical, biological, and nuclear warfare, and it has participated in many covert projects, including experimentation on people without their knowledge. For decades, information on radiation injury to the public was hidden, classified, altered, or destroyed by the PHS. During the radiation disaster at Three Mile Island, they calmly defended the interests of the nuclear industry.

After the April, 1986 catastrophe at the reactor in Chernobyl, some of the food being imported into the U.S. was so highly radioactive that the FDA secretly seized it, to prevent the public from being concerned. The first cow found to have BSE in England was in November, 1986, several months after England's pastures had been heavily contaminated by rainfall carrying radioactive material from Chernobyl, which soaked into the soil and continued to contaminate crops for years (and will continue, for centuries). The number of sick cows increased rapidly to a peak in 1992. Human deaths from the similar disease ("variant CJD") began a few years later.

In June, 2000, a wildfire burned across southern Washington, turning the radioactive vegetation on the Hanford Nuclear Site into radioactive smoke, contaminating a wide area, including farms, dairies, and or-

chards. In 2003, the first cow in the U.S. with BSE was reported, from a dairy a few miles from the Hanford Site.

Beginning in 1946, Bikini Island was used to test atomic bombs. In 1954, they began to test hydrogen bombs in the Pacific; some of the bombs were deliberately designed to vaporize whole islands, so that the effects of radioactive fallout could be studied. In 1954, the first child with kuru was reported in the rainy highlands of New Guinea.

Within two years, hundreds of people in that area (of the Fore tribe) were dying from kuru, with the mortality highest among the women; in some villages, the majority of the women died from the disease, but by 1957 the mortality was falling rapidly. Between 1957 and 1964, 5% of the population of the Fore tribe died of the disease, according to D.C. Gajdusek, who had been sent by the U.S. Army to investigate the disease. Although Gajdusek graduated in 1946 from Harvard medical school as a pediatrician, in his autobiography he said that when he was drafted in 1951, the army assigned him to work in virology. In 1958, Gajdusek became director of the NIH laboratories for neurological and virological research. This was a remarkable achievement for someone who had supposedly only done some scattered field-work in infectious diseases, and whose purpose in going to New Guinea had been to study "child growth and development in primitive cultures." The only published reason I have found that might be a basis for making him head of neurology, was his sending a diseased Fore brain to Fort Detrick in 1957.

Gajdusek claimed to have seen the Fore people eating dead relatives, but his figures show that the disease was already in rapid decline when he arrived. He took photographs which were widely published in the U.S., supposedly showing cannibalism, but 30 years later, he said the photographs showed people eating pork, and that he had seen no cannibalism. (At the time Gajdusek was observing kuru in New Guinea, the influence of "cannibalism" on brain function was already in the news, because of the discovery by J.V. McConnell that the behavior of "trained" flatworms could be transmitted to other worms by chopping them up and feeding them to the naive worms.)

Harvard medical school, in association with the military program centered at Fort Detrick, Fredericksburg, Maryland, was active in biological warfare in the 1940s, and I think it's more plausible to see Gajdusek as a trouble-shooter for the biological warfare establishment, than as a biological researcher. One of his biographers has written that the idea

of associating kuru with scrapie was suggested to him by a veterinarian, and that Gajdusek had responded by claiming to have experiments in progress to test that theory, four years before the experiments were actually made.

In other words, the slow virus theory for which Gajdusek was given the Nobel Prize is scientific junk, which Gajdusek has repeatedly reinterpreted retrospectively, making it seem to have been anticipatory of the prion theory. Whatever actually caused kuru, I think the army was afraid that it was the result of radioactive fallout from one of its bomb tests, and that Gajdusek's job was to explain it away.

I suspect that kuru was the result of an unusual combination of malnutrition (the women were vegetarian) and radiation. In the very short time that Gajdusek spent in New Guinea, he claimed to have done studies to eliminate all of the alternative causes, nutritional, toxic, anthropological, bacterial causes, studies that would normally have required several years of well organized work. I don't think he mentioned the possibility of radiation poisoning.

In 1998 Congress commissioned a study of the health effects of radiation from bomb testing, and although the study examined the effects of only part of the bomb tests, it concluded that they had killed 15,000 Americans. No one has tried to accurately estimate the numbers killed in other countries.

Even very low doses of ionizing radiation create an inflammatory reaction,[2] and there is evidence that the inflammatory state can persist as long as the individual lives; in Japan, the "acute phase" proteins are still elevated in the people who were exposed to radiation from the atomic bombs. The acute phase proteins that are increased by malnutrition and radiation increase the tendency to form amyloid deposits. Strong radiation can even cause, after a delay of more than a year, the development of vacuoles, which are the most obvious feature of the "prion" brain diseases. The persistent inflammatory reaction eventually produces cellular changes, but these were originally overlooked because of the theory that radiation is harmful only when it produces immediate changes in the DNA.

Radiation damage to the brain is most visible early in life, and in old age. In 1955, Alice Stewart showed that prenatal x-rays increase the incidence of brain cancer, leukemia, and other cancers. In 1967, a study in Japanese bomb survivors found that prenatal exposure to radiation

had reduced their head size and brain size. In 1979, Sternglass and Bell showed extremely close correspondence between scores on the SAT and prenatal exposure to radiation.

Serum amyloid A, which can increase 1000-fold under the influence of proinflammatory cytokines, resulting from irradiation, stress, trauma, or infection, is an activator of phospholipase A_2 (PLA_2), which releases fatty acids. Some of the neurodegenerative states, including amyloid-prion diseases, involve activated PLA_2, as well as increases in the toxic breakdown products of the polyunsaturated fatty acids, such as 4-hydroxynonenal. The quantity of PUFA in the tissues strongly determines the susceptibility of the tissue to injury by radiation and other stresses. But a diet rich in PUFA will produce brain damage even without exceptional stressors, when there aren't enough antioxidants, such as vitamin E and selenium, in the diet.

Amyloidosis has traditionally been thought of as a condition involving deposits mainly in blood vessels, kidneys, joints and skin and in extracellular spaces in the brain, and the fact that the "amyloid" stained in a certain way led to the idea that it was a single protein. But as more proteins—currently about 20—were identified in amyloid deposits, it was gradually realized that the deposits can be identified inside cells of many different tissues, before the larger, very visible, extracellular deposits are formed.

There is evidence of a steady increase in the death rate from amyloidosis. It kills women at a younger age than men, often at the age of 50 or 60.

Serum amyloid P is called "the female protein" in hamsters, because of its association with estrogen; castrated (or estrogen treated) males also produce large amounts of it, and its excess is associated with the deposition of amyloid.[3] It can bind other amyloid proteins together, accelerating the formation of fibrils, but this function is probably just a variation of a normal function in immunity, tissue repair, and development.

Estrogen increases the inflammation-associated substances such as IL-6, C-reactive protein, and amyloid, and liberates fatty acids, especially the unstable polyunsaturated fatty acids. It also increases fibrinogen and decreases albumin, increasing the leakiness of capillaries. The decrease of albumin increases the concentration of free fatty acids and tryptophan, which would normally be bound to albumin.

In the U.S. and Europe, livestock are fed large amounts of high-protein feeds, and currently these typically contain fish meal and soybeans. The estrogenic materials in soybeans increase the animals' tendency toward inflammation (with increased serum amyloid).

Officially, BSE appeared because cows were fed slaughter-house waste containing tissues of sheep that had died of scrapie. Scrapie was a nerve disease of sheep, first reported in Iceland in the 18th century. When I was studying the digestive system and nutrition of horses, I learned that it was common for horses in Norway to be fed dried fish during the winter. This abundant food was probably used for sheep, as well as for horses. The extra protein provided by fish meal is still important for sheep in areas where pastures are limited, but it has now become common to use it to increase productivity and growth throughout the lamb, beef, and dairy industries, as well as in most lab chows fed to experimental animals, such as the hamsters used for testing the infectivity of the diseased tissues.

Increased dietary polyunsaturated fatty acids (PUFA) suppress the activity of the ruminal bacteria which are responsible for the hydrogenation-detoxication of PUFA in the animal's diet. This allows the unstable fats, 98 % of which are normally destroyed, to pass into the animals' tissues and milk.

The polyunsaturated fats in fish are very unstable, and when they get past the bacterial saturases (biohydrogenases) in the rumen that normally protect ruminants from lipid peroxidation, they are likely to cause their toxic effects more quickly than in humans, whose antioxidant systems are highly developed. The toxic effects of polyunsaturated fats involve altered (immunogenic) protein structure, decreased energy metabolism, and many inflammatory effects produced by the prostaglandin-like substances. Marine fish are now so generally polluted with dioxin, that in Japan there is a clear association between the amount of fish in a person's diet (their body content of EPA and DHA) and the amount of dioxin in their body.

Radiation and many kinds of poisoning cause early peroxidation of those highly unsaturated fats, and the breakdown products accelerate the changes in the folding and chelating behavior of proteins. The accumulation of altered proteins is associated with the degenerative diseases. The role of toxic metals in brain inflammation is well established (e.g., aluminum, lead, mercury[4–6]).

The "prion hypothesis" has the value of weakening the fanaticism of the DNA-genetics doctrine, but it has some problems. There are now several examples in which other degenerative diseases have been transmitted by procedures similar to those used to test the scrapie agent.[7–9] Experimental controls haven't been adequate to distinguish between the pure prion and its associated impurities. Gajdusek burned a sample of the infective hamster brain to ash, and found that it still retained "infectivity." He argued that there was a mineral template that transmitted the toxic conformation to normal proteins. Others have demonstrated that the active structure of the infective agent is maintained by a carbohydrate scaffolding, or that the infectivity is destroyed by the frequency of ultraviolet light that destroys the active lipid of bacterial endotoxin, lipopolysaccharide.

But simply injuring the brain or other organ (by injecting anything) will sometimes activate a series of reactions similar to those seen in aging and the amyloidoses. When a slight trauma leads to a prolonged or expanding disturbance of structure and function, the process isn't essentially different from transmitting a condition to another individual. The problem is being "transmitted" from the initial injury, recruiting new cells, and passing the disturbed state on to daughter cells in a disturbed form of regeneration. Keloids, hypertrophic scars, are analogous to the dementias in their overgrowth of connective tissue cells: In the aging or injured brain, the glial cells (mainly astrocytes) proliferate, in reparative processes that sometimes become exaggerated and harmful.

When tissue phospholipids contain large amounts of polyunsaturated fatty acids, large amounts of prostaglandins are immediately formed by any injury, including low doses of ionizing radiation. The liberated free fatty acids have many other effects, including the formation of highly reactive aldehydes, which modify DNA, proteins, and other cell components.

Animals which are "deficient" in the polyunsaturated fatty acids have a great resistance to a variety of inflammatory challenges. Their tissues appear to be poor allergens or antigens, since they can be easily grafted onto other animals without rejection. Something related to this can probably be seen in the data of human liver transplants. Women's livers are subjected to more lipid peroxidation than men's, because of the effects of estrogen (increasing growth hormone and free fatty acids, and selectively mobilizing the polyunsaturated fatty acids and increasing

their oxidation). Liver transplants from middle-aged female donors fail much more often (40 to 45%) than livers from male donors (22 to 25%), and other organs show the same effect. The autoimmune diseases are several times as common in women as in men, suggesting that some tissues become relatively incompatible with their own body, after prolonged exposure to the unstable fatty acids. If we consider the healthy function of the immune system to be the removal or correction of injured tissue, it's reasonable to view the random interactions of oxidized fats with proteins as exactly the sort of thing our immune system takes care of.

The serum amyloids A and P and the closely related lipoproteins are considered to be important parts of our "innate immunity," operating in a more general way than the familiar system of specific acquired immunities.

The amyloids and lipoproteins are powerfully responsive to bacterial endotoxin, LPS, and their structural feature that binds it, the "pleated sheet" structure, appears to also be what allows the amyloids to form amorphous deposits and fibrils under some circumstances. Our innate immune system is perfectly competent for handling our normal stress-induced exposures to bacterial endotoxin, but as we accumulate the unstable fats, each exposure to endotoxin creates additional inflammatory stress by liberating stored fats. The brain has a very high concentration of complex fats, and is highly susceptible to the effects of lipid peroxidative stress, which become progressively worse as the unstable fats accumulate during aging.

More than 60 years ago, a vitamin E deficiency was known to cause a brain disease, sometimes associated with sterility and muscular dystrophy. The symptoms of the brain disease were similar to those of "mad cow disease," and the condition is now usually called "crazy chick disease." Veterinarians are usually taught that it is caused by a selenium deficiency, but it is actually the result of an excess of PUFA in the diet, and is exacerbated by increased iron or other oxidants, and prevented by increased vitamin E, selenium, or substitution of saturated fats for the unsaturated.

Terminology, established by tradition and thoughtless memorization, obscures many of the commonalities in the various brain diseases. Brain inflammation,[10,11] myelination disorders, edema, overgrowth of the astroglia, and circulatory changes are common occurrences in most

of the degenerative encephalopathies, but traditional textbook descriptions have created the impression that each disease is pathologically very distinct from the others. The current classification of "the prion diseases" is reifying a group of symptoms that aren't specific to any specific known cause. And standard laboratory procedures for preparing brain sections for microscopic examination may cause brain cells to shrink to 5 % of their original volume,[12] so the objectivity of pathological studies shouldn't be over-estimated.

According to a 1989 study,[13] 13 % of the people who had died from "Alzheimer's disease" actually had CJD. Between 1979 and 2000, the number of people dying annually from Alzheimer's disease increased 50-fold. Very competent neuropathologists differ radically in their descriptions of the dementia epidemic.

By some tests, the "prion" resembles the LPS endotoxin. One of the interesting developments of the prion theory is that a particular structure that appears when the prion becomes toxic, the "beta pleated sheet," is also a feature of most of the normal proteins that can form amyloid, and that this structure is directly related to binding and eliminating the bacterial LPS. If the prion theory is correct about the conversion of a normal protein into the pleated sheet, it isn't necessarily correct about the incurability of the condition. The innate immune system should be able to inactivate the prion just as it does the bacterial endotoxin, if we remove the conditions that cause the innate immune reaction to amplify the inflammation beyond control.

In the prion diseases, the severely damaged brain appears to have a "pathological overactivity" of the serotonergic systems.[14] This is an interesting parallel to Alzheimer's disease, since it has been known for several years that the blood platelets have an increased tendency to release serotonin in that more common form of dementia. Serotonin itself is toxic to nerves, and is part of the adaptive system that gets out of control during prolonged inflammation. Serotonin is an important activator of the phospholipases.

The modification of proteins' structure by glycosylation is involved in the development of the toxic form of the "prionic" protein, as well as in all the degenerative processes of aging. Until the ability to use sugar is impaired, cells produce enough carbon dioxide to protect proteins against random glycation, but with each exposure to free polyunsaturated fatty

acids, the ability to use glucose is damaged. In the dementias, the brain has a greatly reduced ability to use glucose.

One of estrogen's central effects is to shift metabolism away from the oxidation of glucose, decreasing carbon dioxide production. There is a much higher incidence of Alzheimer's disease in women, and estrogen exposure exacerbates all of the changes that lead to it, such as shifts in nerve transmitters, increased vascular leakiness, and the increased production of the acute phase proteins.

Everything that is known about the "always fatal" prionic diseases, the diseases of disturbed protein folding, suggests that they can be avoided and even reversed by systematically reversing the processes that amplify inflammation.

People who take aspirin, drink coffee, and use tobacco, have a much lower incidence of Alzheimer's disease than people who don't use those things. Caffeine inhibits brain phospholipase, making it neuroprotective in a wide spectrum of conditions. In recent tests, aspirin has been found to prevent the misfolding of the prion protein, and even to reverse the misfolded beta sheet conformation, restoring it to the harmless normal conformation. Nicotine might have a similar effect, preventing deposition of amyloid fibrils and disrupting those already formed.[15] Vitamin E, aspirin, progesterone, and nicotine also inhibit phospholipase, which contributes to their antiinflammatory action. Each of the amyloid-forming proteins probably has molecules that interfere with its toxic accumulation.

Thyroid hormone, vitamins A and E, niacinamide (to inhibit systemic lipolysis), magnesium, calcium, progesterone, sugar, saturated fats, and gelatin all contribute in basic ways to prevention of the inflammatory states that eventually lead to the amyloid diseases. The scarcity of degenerative brain disease in high altitude populations is consistent with a protective role for carbon dioxide.

The relatively sudden acceptability of the idea of non-genetic transmission doesn't mean that Lamarck has been rehabilitated by the scientific establishment; it could just be that it's the most politically acceptable way to explain the outbreaks of deadly disease caused by the industrialization of foods and the exposure of the population to dangerous levels of radiation.

Bleeding, Clotting, Cancer

Ray Peat's Newsletter, 2006

WHEN science became a sort of "profession," in the 19th century, the old "natural philosophy" of Newton's time began to subdivide into many specialties. At that time, medicine had some general theories to account for deviations from good health, such as the theory of the four humors and their balance, but as those general theories disappeared, they weren't replaced by any single scientific understanding of the nature of good health and disease. Medical education has convinced doctors and the public that the reasons for suffering, disability and death are mostly known, and that when medical experts agree to give a condition a name, there must be some clear scientific evidence behind that disease name.

That mystique of diagnosing disease (specific, concrete, reified disease) was so strong that when Hans Selye noticed (in the 1930s) something that underlies all sickness (he first called it the "syndrome of being sick"), he was disregarded and disrespected, at least until his dangerous perceptions could be trimmed, distorted, and subsumed under some proper medical categories. Selye observed that stress causes internal bleeding (in lungs, adrenals, thymus, intestine, salivary and tear glands, etc.), but instead of trying to understand what that means for the control of sickness, the medical schools and journals have offered concrete, fragmentary, and false explanations for his observations. "Stomach acid" causes bleeding in the stomach and duodenum; stuff leaking out of the brain gets the blame for some cases of systemic bleeding, stuff leaking out of the uterus, for other cases, and so on. Selye's observations have been rendered harmless (to medicine) by these falsely concrete explanations. While conventional medicine propagated its medical fantasies, it characterized Selye's work as "controversial."

In many cases, "diagnosis" consists of what could, at best, be called an educated guess, with no attempt to find evidence to support it. Obviously, if every doctor in the country is guessing wrong about certain deadly conditions, lots of people will die, and no one will see the need to even study the subject, since it has a definite name and an explanation that seems to satisfy.

Instead of finding pseudo-reasons for the bleeding abnormalities caused by stress, it would be good to look freshly at the nature of blood and its circulation. It might turn out that it's a way to expand our understanding of the stress reaction.

Most people are aware of some of the variations of bleeding and clotting that occur commonly. Bleeding gums, nose-bleeds, menstruation and its variations, and the spontaneous bruising (especially on the thighs) that many women have premenstrually, are familiar events that don't seem to mean much to the medical world. Sometimes nosebleeds are clearly stress-related, but the usual "explanation" for that association is that high blood pressure simply blows out weak blood vessels. Bleeding gums are sometimes stress related, but high blood pressure is seldom invoked to explain that problem.

The whole issue of blood vessel fragility is usually disposed of as a "genetic trait," or a result of old age. This is part of a general tendency to think of the blood vessels as an anatomically fixed, "congenital," and genetically determined system. At least until recently, nearly all physicians have called aneurysms "congenital defects." But varicose veins are merely low-pressure analogs of arterial aneurysms, and they obviously develop under specific conditions, such as pregnancy and malnutrition. Spider veins are another anatomical variation that commonly appears under the influence of estrogen. Subarachnoid hemorrhages, which can put pressure on the brain, are usually considered to result from a ruptured aneurysm, and these hemorrhages are twice as common in women as in men, and probably result from a hormone imbalance.

Menstrual bleeding is a good place to start the investigation of bleeding problems, since its relatively harmless abnormalities are physiologically related to some very serious health problems, such as pregnancy bleeding, abruptio placentae, and eclampsia. Women who die from eclampsia have been found to have massively clotted blood vessels in their brains, but the variety of names for the pregnancy disorders have prevented most people from thinking of pregnancy as a time when there is a high risk of the "thrombohemorrhagic disorders," a time when the clotting system is under stress. (For about fifteen years after Selye coined the term, only he and some Russians were publishing research on it, and Americans still don't show much interest in the subject.)

Women with a chronic menstrual problem resulting from progesterone deficiency often continue to bleed each month even when they

are pregnant, and these women tend to develop toxemia, and to have a high incidence of pregnancy complications, and to deliver premature, poorly developed babies.

In 1933 James Shute was recommending the use of vitamin E for preventing the clotting problems associated with pregnancy, that often lead to miscarriage. He based his work on animal studies, that led to vitamin E's being known as the "fertility vitamin." Later, his sons Wilfred and Evan reported that vitamin E could prevent heart attacks, birth defects, complications of diabetes, phlebitis, hypertension, and some neurological problems.

Later, referring to the decades of hostility of the medical establishment to vitamin E, Dr. Shute said "…an obstetrician was unduly hardy and audacious to try it." The spectrum of vitamin E's protective effects (like those of aspirin) has been consistently misrepresented in the medical literature.

Hematomas in many organs (pituitary, kidney, pancreas, liver, even around the abdominal muscles) can occur because of hormone imbalances in these difficult pregnancies. Tom Brewer's demonstration that a good diet, with abundant protein, can prevent and cure pregnancy toxemia, is practically unknown in the medical world, though a protein deficiency has been shown to increase the risk of blood clots under many other circumstances besides pregnancy.

Abruptio placentae (premature detachment of the placenta) has often been blamed on the use of vitamin E, because of vitamin E's reputation for preventing abnormal clotting, though the evidence tends to suggest instead that vitamin E (like aspirin) reduces the risk of pregnancy-related hemorrhaging.

One of the deadly clotting conditions related to childbirth has been called "pregnancy anaphylaxis," but it is more often called "amniotic fluid embolism," despite the fact that amniotic fluid injected intravenously is harmless,[1] and only by grinding up and injecting massive amounts of the pregnancy membranes can the clotting system be disturbed. The term is really a criminal misnomer, serving to blame a preventable clotting/shock disorder on the patient.

"Consumption coagulopathy" refers to the bleeding that follows excessive activation of the clotting system, combined with a defensive dissolving of the clots, when finally the fibrinogen or other elements of the clotting system have been depleted, consumed. A blood test can

show when clot degradation products are being produced too rapidly, even while a person has no symptoms, so there should be time for the accelerated clotting to be controlled, before major thromboses and bleeding and shock have developed.

In 1936 Albert Szent-Györgyi reported that some chemicals in lemon juice, which he called vitamin P (or citrin), would prevent purpura, subcutaneous capillary bleeding. By 1938, he had decided that citrin, (which he now called bioflavonoid) probably wasn't a vitamin, and that its action was more like that of a drug, substituting for a natural regulatory factor that was missing. Later research has confirmed that view, showing that the bioflavonoids inhibit the enzyme hyaluronidase, which degrades the "ground substance" of connective tissues. At least one natural endogenous inhibitor of hyaluronidase has now been identified. The basement membrane that surrounds and unites the endothelial cells of capillaries is largely hyaluronic acid and collagen. It isn't thrombogenic,[2] despite the common belief that collagen is intrinsically a clot instigator. The breakdown of this ground substance is involved in growth and reproduction, so an excess of bioflavonoids in the diet could conceivably interfere with fertility and fetal development. Some bioflavonoids have been prescribed for menstrual problems, and are probably useful when the physiological inhibitor isn't adequate.

Hyaluronidase is activated by shock, and also by estrogen. Both hyaluronidase and estrogen have been used in plastic surgery to "expand" tissue, weakening it and allowing it to be enlarged. During aging, hyaluronic acid (the major water-retaining component of connective tissue that's broken down by hyaluronidase) decreases in the connective tissues, but increases in the blood stream. Shock allows hyaluronic acid to increase in the serum. Fragments of degraded hyaluronic acid are pro-inflammatory.

In the 1940s Hans Selye studied the steroid hormones in a comprehensive way, defining their actions and interactions. At that time he found that progesterone protected broadly against stress, and that a large dose of estrogen created a condition that duplicated the initial shock phase of the stress reaction. Later animal studies showed that estrogen quickly causes enlargement of the adrenal glands, followed by bleeding, and, with large and continuous doses, death of the adrenal cells.

Estrogen promotes vascular permeability by a variety of mechanisms. Serotonin, histamine, lactic acid, and various cytokines and

prostaglandins contribute to the leakage stimulated by estrogen, trauma, irradiation, poisoning, oxygen deprivation, and other factors that can induce shock. Even exercise, mental stress, and aging can increase the tendency of capillaries to leak.

Progesterone and cortisol protect against shock and stress partly by maintaining the resistance and integrity of the capillaries, preventing leakage of blood materials into the tissues. The maintenance of the capillary barrier probably also prevents substances from the extracellular matrix from triggering the clotting systems.

Clots are formed when soluble fibrinogen polymerizes, condenses, and becomes insoluble. Even before the particles of fibrin become insoluble, a clot-dissolving system is continuously breaking it down into small peptides. These peptides tend to cause capillaries to leak. If a massive amount of fibrinogen and fibrin leak out of capillaries, clots are formed outside capillaries, and the peptides released in the process of cleaning up this debris contribute to further leakage, and to inflammation. The inflammation stimulates the production of collagen-rich connective tissue, and a fibrotic tissue replaces the functional tissues. Many of Hans Selye's experiments explored the conditions in which inflammation, exudation, and fibrosis developed, sometimes ending with calcification of the region.

The presence of fibrin in the extracellular matrix interferes with the differentiated functioning of cells, which depend on their contact with a normal matrix. When healing and regeneration occur in the normal matrix, the remodeling of the tissue involves the breakdown of collagen, which releases peptides with antiinflammatory, antiangiogenic and antiinvasive actions. When fibrin is present, the remodeling process releases peptides that increase cell growth, invasiveness, inflammation, and the production of new blood vessels, which in turn become leaky.

Leakage of fluid out of the blood is one of the main features of shock, and at first it is mainly the loss of water and volume that creates a problem, by reducing the oxygenation of tissue and increasing the viscosity of the remaining blood. Blood becomes more concentrated during strenuous exercise, during the night, and in the winter, increasing the viscosity, and increasing the risk of strokes and other thrombotic problems. The absence of light causes the metabolic and hormonal changes typical of stress.

Tom Brewer and his associates showed that pregnancy toxemia involves inadequate blood volume, and that using extra sodium can alleviate the symptoms, including preventing albuminuria, one of the most characteristic signs of toxemia/preeclampsia. (Besides causing loss of albumin through leaky capillaries, estrogen also inhibits its synthesis by the liver; the loss of colloid osmotic pressure in hypoalbuminemia has many consequences, including disturbances of blood lipids.) Estrogen's action in toxemia of pregnancy is paralleled by the fact that blood viscosity is highest at the time of ovulation during the normal monthly cycle.

In the healthy person, some of the fibrin that is constantly being formed is deposited on the inside of blood vessels (and on the surfaces of blood cells), and this layer forms an important part of the capillary's resistance to leaking. A.L. Copley, who pioneered the study of hemorrheology, called this the "endoendothelial layer." This layer probably contains albumin, too, in close association with the (carbohydrate) "glycocalyx" of the endothelial cell surface. Disturbances that accelerate the formation and dissolution of the fibrin layer can be detected by an increase in the concentration of the fibrin degradation products (FDP, or D-dimers) in the blood, even before any symptoms have appeared.

Although Selye described shock as the first (potentially lethal) phase of stress, usually followed by the corrective adaptive processes, it's useful to think of aging in terms of a lingering partial state of shock, in which adaptation is less than perfect.

The loss of blood volume through leaky capillaries tends to be self-aggravating. The concentrated and viscous blood doesn't flow as well through the capillaries, and this energy deprivation leads to increased leakiness of the cells, and to swelling of the endothelial cells, decreasing the internal diameter of the small blood vessels. The energy-deprived state increases lactic acid, adrenaline, and free fatty acids, all of which contribute to increased leakiness and impaired circulation.

In the bowel, the capillary malfunction increases the absorption of endotoxin, which intensifies the systemic energy problem. (Polyunsaturated oils, especially fish oil, damage the bowel capillaries, allowing more endotoxin to be absorbed.)

In the uterus, increased viscosity of the blood impairs the delivery of oxygen and nutrients to the fetus, retarding its development. Dilution of the blood under the influence of progesterone reduces the hematocrit,

helping to compensate for the viscosity; in toxemic pregnancies this isn't sufficient to maintain normal viscosity and perfusion.

In the brain, hyperviscosity contributes to dementia. In the lung, to edema and reduced oxygenation ("shock lung," "wet lung," respiratory distress; this lung edema is a major cause of mortality in pregnancy). In the pancreas, to inflammation, and to the release of proteolytic enzymes, impairing the clotting system even more.

During the development of cancer, hyperviscosity (and the associated hypoxia) contributes to the tumor's deranged metabolism, tending to increase its production of ammonia, clotting factors, and other stress-inducing toxins.

Factors that increase the fluidity of the blood protect against all of the thrombohemorrhagic conditions, and are especially protective against the estrogen-promoted cancers. Progesterone decreases the production of fibrinogen, and increases the volume of the blood and the flexibility of the red blood cells, increasing the ability of blood to flow freely, and it also decreases the leakiness of capillaries. Hypothyroid people (who tend to have low progesterone and high estrogen) are highly susceptible to heart disease and cancer, and have abnormally viscous blood. Hyperthyroid people have unusually fluid blood. Hypothyroidism increases the leakiness of capillaries, and decreases the amount of albumin in the blood. Albumin itself decreases the permeability of blood vessels.

In hypothyroidism and under the influence of estrogen, there is a chronic increase of free fatty acids, and the free fatty acids are an important factor in increasing the production of fibrinogen,[3] and in blocking fibrinolysis.[4] If the body's stores of fat are largely polyunsaturated fats, the free fatty acids will combine with the fibrin as it polymerizes, making the clots especially resistant to dissolution.

In the 1940s, Melvin Knisely noticed that all seriously sick people had "sludged" blood, that can be observed microscopically in the small blood vessels on the surface of the person's eye. The cells tend to stick together, producing a sludgy appearance and slow flow. This probably corresponds to increased viscosity of the plasma, increased red cell sedimentation rate, increased fibrinogen, decreased albumin, and decreased thyroid and progesterone. Clumped red cells, when separated under the microscope, appear to be bound together by fine filaments, possibly of fibrin.

Aspirin is known to have a variety of anticancer activities, including the prevention of metastasis, and some people have reasoned that the

clotting process simply helps migrating cancer cells to become anchored. However, the clotting process is normally part of the healing and repair processes, and I think the role of the fibrin clotting system in cancer is that the breakdown products of fibrin are growth-promoters, and that their presence in the extracellular matrix in large quantity, distorting the normal composition of the matrix, is what causes the formation of a tumor. It's the leakage of the fibrin into the extracellular matrix that leads to the development of tumors.

Heparin, a natural anticoagulant, is currently being tested as an anticancer agent.

All of the factors that promote stable oxidative energy production protect against the coagulative derangements, largely by preventing capillary leakage, and it now seems that these processes protect against cancer as well as protecting against all of the stress-related degenerative and inflammatory diseases.

Since hyperventilation can increase capillary leakage and cause the blood to become more concentrated, breathing carbon dioxide (breathing in a bag) should help to restore capillary function.

Since the blood becomes more concentrated, viscous, and clottable during the night (especially during long winter nights), the risk of a heart attack or stroke would probably be reduced by drinking orange juice before getting out of bed (and at bed-time), to dilute the blood and decrease adrenaline and the free fatty acids, which contribute to the increased tendency to form clots in the morning.[5,6]

Things to reduce the stress-related coagulopathies: Sugar and niacin to minimize the liberation of fatty acids, progesterone and thyroid to protect against estrogen and to avoid hypoglycemia (which increases adrenaline and free fatty acids and accelerates clotting), magnesium and gelatin (or glycine), to protect against intracellular calcium overload and hypoxia, and vitamin E and salicylic acid for antiinflammatory effects, are major nutrients that protect the circulatory system against clotting, bleeding, edema, and tumefaction.

Even on the mornings that you don't drop dead, there is reduced adaptive capacity and functional impairment before eating breakfast. For example, men who went for a run before breakfast were found to have broken chromosomes in their blood cells, but if they ate breakfast before running, their chromosomes weren't damaged.

Blocking Tissue Destruction

Ray Peat's Newsletter, 2006

THERE always seems to be a rough balance between tissue regeneration and tissue degeneration, with growth and repair occurring when the equilibrium shifts in one direction, and with atrophy or degeneration occurring when the balance shifts in the other direction. If we can understand the mechanisms of atrophy, and how to retard or to block tissue destruction, then we can restore the balance to a degree which might allow regeneration to occur, even if we don't clearly understand the mechanisms of growth.

Skin and bones are such different types of tissue that it will be useful to start with them, because if we can see similar processes of degeneration or regeneration in them, then the chances are good that the same processes will occur in other tissues too. Bone is a relatively stable tissue, while skin is a tissue whose cells divide rapidly.

It is common medical knowledge that cortisone and related glucocorticioid-type hormones cause skin to atrophy, becoming thinner. Using topical applications of a synthetic derivative of cortisone, CM Papa and A M. Kligman showed that the atrophy extended to the pigment cells, reducing their size and eliminating most of their dendritic branches. Some animal studies have found that estrogen caused the skin to become thinner. The other steroids they tested, progesterone, testosterone, and pregnenolone, acted in the opposite direction, making aged and atrophied skin thicker and more regular. They also made the pigment cells larger, and increased their branching. Since these hormones were already known to have protective actions against cortisone and estrogen, these results were not too surprising, though they did directly contradict the claims of people who made estrogen-containing cosmetics.

Since progesterone and pregnenolone do not cause healthy, young skin to thicken, their effect in damaged skin is probably partly to replace the deficiency of that type of steroid which occurs with aging, and to offset the damaging effects of the catabolic hormones, whose influence does not decrease with age.

Many years ago it was found that in old age a woman's estrogens were increased relative to the 17-keto steroids adrenal androgens. Later, it was found that the conversion of androgen to estrogen increases with age in

both men and women, and that this occurs largely in fat cells. Several years ago, P. K. Siiteri found that low thyroid modified the enzymes of fat cells in a way that would tend to increase the conversion of androgen to estrogen. More recently, it was found that adding progesterone to the enzymes had the opposite effect of aging and hypothyroidism, protecting the androgen from conversion to estrogen. These researchers (C. J. Newton and colleagues, of London) concluded that the decreased output of progesterone after the menopause might account for the increased production of estrogen. Since progesterone declines in aging men, too, this could account for the same process in men.

Vitamin A's effect on the skin opposes that of estrogen. There are several mechanisms that could account for this. Vitamin A is used in the formation of steroids, and since the skin is a major site of steroid metabolism, vitamin A might help to maintain the level of the anti-catabolic steroids. A deficiency of vitamin A causes excessive release of the lysosomal enzymes, acid hydrolases, resulting in tissue catabolism. Also, vitamin A is necessary for the proper differentiation of cells in skin and other membranes. A deficiency tends to cause an increased rate of cell division, with the production of abnormal cells, and a substitution of keratinized cells for other types. Estrogen also promotes keratinization and speeds cell division. A deficiency of vitamin A can cause leukoplakia in the mouth and on the cervix of the uterus; although this is considered "pre-cancerous," I have found it to be very easily reversible, as I have discussed elsewhere. I suspect that the intracellular fiber, keratin, is produced when a cell can't afford to do anything more complex. Adequate vitamin A speeds protein synthesis, and allows it to be used more efficiently.

Prolactin (which is promoted by estrogen, and inhibited by progesterone) increases with stress and with age. It probably affects every tissue, but it seems to have its greatest effects on the secretory membranes. It is known to have strong effects on the kidney, gut and skin (sweat and oil glands, hair follicles, and feathers in birds), and on the gills of fish. Its involvement with milk production suggests that it might mobilize calcium from bones, and in fact it does contribute to osteoporosis. This was foreseen by G. Bourne, in his book on the metabolism of hard tissues, when he suggested that estrogen, acting through the pituitary, might be expected to promote osteoporosis.

Since reading Bourne's book, I have doubted that it was rational to use estrogen to prevent osteoporosis, especially when it is known to be carcinogenic and when the ratio of estrogen to androgens and progesterone increases after menopause. Now that several publications have appeared clearly showing that estrogen increases prolactin, that prolactin increases with cancellous bone; adrenal androgens. Thyroid rate of formation, overall metabolic rate.

Arthritis and Natural Hormones

A very healthy 71 year-old man was under his house repairing the foundation, when a support slipped and let the house fall far enough to break some facial bones. During his recovery, he developed arthritis in his hands. It is fairly common for arthritis to appear shortly after an accident, a shock, or surgery, and Han Selye's famous work with rats shows that when stress exhausts the adrenal glands (so they are unable to produce normal amounts of cortisone and related steroid hormones), arthritis and other "degenerative" diseases are likely to develop.

But when this man went to his doctor to "get something for his arthritis," he was annoyed that the doctor insisted on giving him a complete physical exam, and wouldn't give him a shot of cortisone. The examination showed low thyroid function, and the doctor prescribed a supplement of thyroid extract, explaining that arthritis is one of the many symptoms of hypothyroidism. The patient agreed to take the thyroid, but for several days he grumbled about the doctor "fixing something that wasn't wrong" with him, and ignoring his arthritis. But in less than two weeks, the arthritis had entirely disappeared. He lived to be 89, without a recurrence of arthritis. (He died iatrogenically, while in good health.)

Selye's work with the diseases of stress, and the anti-stress hormones of the adrenal cortex, helped many scientists to think more clearly about the interaction of the organism with its environment, but it has led others to focus too narrowly on hormones of the adrenal cortex (such as cortisol and cortisone), and to forget the older knowledge about natural resistance. There are probably only a few physicians now practicing who would remember to check for hypothyroidism in an arthritis patient, or in other stress-related conditions. Hypothyroidism is a common cause of adrenal insufficiency, but it also has some direct effects on joint tissues.

In chronic hypothyroidism (myxedema and cretinism), knees and elbows are often bent abnormally.

By the 1930's, it was well established that the resistance of the organism depended on the energy produced by respiration under the influence of the thyroid gland, as well as on the adrenal hormones, and that the hormones of pregnancy (especially progesterone) could substitute for the adrenal hormones. In a sense, the thyroid hormone is the basic anti-stress hormone, since it is required for the production of the adrenal and pregnancy hormones.

A contemporary researcher, F. Z. Meerson, is putting together a picture of the biological processes involved in adapting to stress, including energy production, nutrition, hormones, and changes in cell structure.

While one of Selye's earliest observations related gastrointestinal bleeding to stress, Meerson's work has revealed in a detailed way how the usually beneficial hormone of adaptation, cortisone, can cause so many other harmful effects when its action is too prolonged or too intense.

Some of the harmful effects of the cortisone class of drugs (other than gastro-intestinal bleeding) are: Hypertension, osteoporosis, delayed healing, atrophy of the skin, convulsions, cataracts, glaucoma, protruding eyes, psychic derangements, menstrual irregularities, and loss of immunity allowing infections (or cancer) to spread.

While normal thyroid function is required for the secretion of the adrenal hormones, the basic signal which causes cortisone to be formed is a drop in the blood glucose level. The increased energy requirement of any stress tends to cause the blood sugar to fall slightly, but hypothyroidism itself tends to depress blood sugar.

The person with low thyroid function is more likely than a normal person to require cortisone to cope with a certain amount of stress. However, if large amounts of cortisone are produced for a long time, the toxic effects of the hormone begin to appear. According to Meerson, heart attacks are provoked and aggravated by the cortisone produced during stress. (Meerson and his colleagues have demonstrated that the progress of a heart attack can be halted by a treatment including natural substances such as vitamin E and magnesium.)

While hypothyroidism makes the body require more cortisone to sustain blood sugar and energy production, it also limits the ability to produce cortisone, so in some cases stress produces symptoms resulting

from a deficiency of cortisone, including various forms of arthritis and more generalized types of chronic inflammation.

Often, a small physiological dose of natural hydrocortisone can help the patient meet the stress, without causing harmful side-effects. While treating the symptoms with cortisone for a short time, it is important to try to learn the basic cause of the problem, by checking for hypothyroidism, vitamin A deficiency, protein deficiency, a lack of sunlight, etc. (I suspect that light on the skin directly increases the skin's production of steroids, without depending on other organs. Different steroids probably involve different frequencies of light, but orange and red light seem to be important frequencies.) Using cortisone in this way, physiologically rather than pharmacologically, it is not likely to cause the serious problems mentioned above.

Stress-induced cortisone deficiency is thought to be a factor in a great variety of unpleasant conditions, from allergies to ulcerative colitis, and in many forms of arthritis. The stress which can cause a cortisone deficiency is even more likely to disturb formation of progesterone and thyroid hormone, so the fact that cortisone can relieve symptoms does not mean that it has corrected the problem.

According to the Physicians' Desk Reference, hormones similar to cortisone are useful for treating rheumatoid arthritis, post-traumatic osteoarthritis, synovitis of osteoarthritis, acute gouty arthritis, acute nonspecific tenosynovitis, psoriatic arthritis, ankylosing spondylitis, acute and subacute bursitis, and epicondylitis.

Although cortisone supplementation can help in a great variety of stress-related diseases, no cure will take place unless the basic cause is discovered. Besides the thyroid, the other class of adaptive hormones which are often out of balance in the diseases of stress, is the group of hormones produced mainly by the gonads: the "reproductive hormones." During pregnancy these hormones serve to protect the developing baby from the stresses suffered by the mother, but the same hormones function as part to the protective anti-stress system in the non-pregnant individual, though at a lower level.

Some forms of arthritis are known to improve or even to disappear during pregnancy. As mentioned above, the hormones of pregnancy can make up for a lack of adrenal cortex hormones. During a healthy pregnancy, many hormones are present in increased amounts, including the thyroid hormones. Progesterone, which is the most abundant hormone

of pregnancy, has both anti-inflammatory and anesthetic actions, which would be of obvious benefit in arthritis.

There are other naturally anesthetic hormones which are increased during pregnancy, including DHEA, which is being studied for its anti-aging, anti-cancer, and anti-obesity effects. (One of the reasons that is frequently given for the fact that this hormone hasn't been studied more widely is that, as a natural substance, it has not been monopolized by a drug patent, and so no drug company has been willing to invest money in studying its medical uses.) These hormones also have the ability to control cell division, which would be important in forms of arthritis that involve invasive tissue growth.

While these substances, so abundant in pregnancy, have the ability to substitute for cortisone, they can also be used by the adrenal glands to produce cortisol and related hormones. But probably the most surprising property of these natural steroids is that they protect against the toxic side-effects of excessive adrenal hormones. And they seem to have no side-effects of their own; after about fifty years of medical use, no toxic side effects have been found for progesterone or pregnenolone.

Pregnenolone is the material the body uses to form either progesterone or DHEA. Others, including DHEA, haven't been studied for so long, but the high levels which are normally present in healthy people would suggest that replacement doses, to restore those normal levels, would not be likely to produce toxic side effects. And, considering the terrible side effects of the drugs that are now widely used, these drugs would be justifiable simply to prevent some of the toxic effects of conventional treatment.

It takes a new way of thinking to understand that these protective substances protect against an excess of the adrenal steroids, as well as making up for a deficiency. Several of these natural hormones also have a protective action against various poisons; Selye called this their "catatoxic" effect.

Besides many people whose arthritis improved with only thyroid supplementation, I have seen 30 people use one or more of these other natural hormones for various types of arthritis, usually with a topical application. Often the pain is relieved within a few minutes. I know of several other people who used progesterone topically for inflamed tendons, damaged cartilage, or other inflammations. Only one of these, a woman with rheumatoid arthritis in many joints, had no significant

improvement. An hour after she had applied it to her hands and feet, she enthusiastically reported that her ankle had stopped hurting, but after this she said she had no noticeable improvement.

We often hear that "there is no cure for arthritis, because the causes are not known." If the cause is an imbalance in the normal hormones of adaptation and resistance, then eliminating the cause by restoring balance will produce a true cure. But if it is more profitable to sell powerful drugs than to sell the nutrients needed to form natural hormones (or to supplement those natural hormones) we can't expect the drug companies to spend any money investigating that sort of cure. And at present the arthritis market amounts to billions of dollars in drug sales each year.

Bone Density: First Do No Harm

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No topic can be understood in isolation. People frequently ask me what they should do about their diagnosed osteoporosis/osteopenia, and when they mention "computer controlled" and "dual photon x-ray" bone density tests, my attention tends to jump past their bones, their diet, and their hormones, to the way they must perceive themselves and their place in the world. Are they aware that this is an x-ray that's powerful enough to differentiate very opaque bones from less opaque bones? The soft tissues aren't being studied, so they are allowed to be "overexposed" until they appear black on the film. If a thick area like the thigh or hip is to be measured, are they aware that the x-ray dose received at the surface where the radiation enters might be 20 times more intense than the radiation that reaches the film, and that the 90 or 95 % of the missing energy has been absorbed by the person's cells? If I limited my response to answering the question they thought they had asked me, I would feel that I had joined a conspiracy against them. My answer has to assume that they are really asking about their health, rather than about a particular medical diagnosis.

Neurologists are famous for making exquisitely erudite diagnoses of problems that they can't do anything to remedy. The owners of expensive dual photon x-ray absorptiometer diagnostic machines are in a very different position. The remedies for osteoporosis are things that everyone should be doing, anyway, so diagnosis makes no difference in what the physician should recommend to the patient.

Most often, estrogen is prescribed for osteoporosis, and if the doctors didn't have their bone density tests, they would probably prescribe estrogen anyway, "to protect the heart," or "to prevent Alzheimer's disease." Since I have already written about estrogen and those problems, there's no need to say more about it here, except that estrogen is the cause of a variety of tissue atrophies, including the suppression of bone formation.[1]

General Electric, a major advocate of x-ray screening for osteoporosis and breast cancer, has advertised that 91 % of breast cancers could be cured if everyone used their technology. Breast cancer has not decreased despite the massive application of the technology, though the U.S. government and others (using crudely deceptive statistics) claim that the

War on Cancer is being won. Similarly, during the last decades when the "high technology" x-ray machines have been more widely used, the age-specific incidence of osteoporosis has increased tremendously. This apparently includes a higher rate of shortening of stature with aging than in earlier generations.[2]

I think there are several reasons for avoiding x-ray tests of bone density, besides the simple one that everyone should eat a bone-protective diet, regardless of the present density of their bones.

Even seemingly identical x-ray machines, or the same machine at a different time, can give very different estimates of bone density.[3–10] Radiologists evaluating the same images often reach very different conclusions.[11] Changes in the tissue water and fat content can make large differences in apparent bone density,[12] and estrogen, which affects those, could appear to cause improved bone density, when it is merely causing a generalized inflammatory condition, with edema. A machine that is accurate when measuring an aluminum model, won't necessarily give meaningful results when the composition of the tissue, including the bone marrow, has changed. Calcification of soft tissues can create the impression of increased bone density.[13] Studies of large groups of people show such small annual losses of bone density (around 1 %), especially in the neck of the femur (which is important in hip fractures) that the common technical errors of measurement in an individual seem very large.

- Ultrasound devices can do an extremely good job of evaluating both bone density and strength,[14–16] rather than just density.
- Ultrasound stimulates bone repair.
- X-rays accelerate the rate of bone loss.
- X-rays do their harm at any dose; there is no threshold at which the harm begins.

X-ray damage is not limited to the area being investigated. Deflected x-rays affect adjacent areas, and toxins produced by irradiated cells travel in the bloodstream, causing systemic effects. Dental x-rays cause thyroid cancer and eye cancer. Recent experiments have shown that low doses of radiation cause delayed death of brain cells. The action of x-rays produces tissue inflammation, and diseases as different as Alzheimer's disease and heart disease result from prolonged inflammatory processes.

I have never known a physician who knew, or cared, what dose of radiation his patients were receiving. I have never known a patient who could get that information from their doctors.

The radiation exposure used to measure bone density may be higher (especially when the thigh and hip are x-rayed) than the exposure in dental x-rays, but dental x-rays are known to increase the incidence of cancer. Often, dentists have their receptionists do the x-rays, which probably doesn't matter, since the dentist is usually no more concerned than the receptionist about understanding, and minimizing, the dose. Even radiological specialists seldom are interested in the doses they use diagnostically.

It was only after a multitude of dentists had a finger amputated that it became standard practice to ask the patient to hold the film, while the dentist stood safely back away from the rays.

Just after the beginning of the century, Thomas Edison was helping to popularize x-rays, but the horrible death of his chief technician turned Edison into an enemy of the technology. By the 1940s, the dangers of radiation were coming to be understood by the general public, and it was only the intervention of the U.S. government, to popularize atomic bombs and nuclear power, that was able to reverse the trend.

In 1956 and 1957, Linus Pauling was the only well known scientist who opposed the government's policies. The government took away his passport, and his opportunities to write and speak were limited by a boycott imposed by a variety of institutions, but instigated by the nuclear industry and its agent, the Atomic Energy Commission. The government which considered Pauling a threat to national security, had placed thousands of German and Hungarian "ex"-Nazis in high positions in industry and government agencies, after protecting them from prosecution as war criminals. The official government policy, directed by the financier Admiral Strauss who controlled the Atomic Energy Commision, was to tell the public that radiation was good. Their extreme secrecy regarding their radiation experiments on Americans, however, indicated that they were aware of the malignant nature of their activities; many of the records were simply destroyed, so that no one could ever know what had been done. Scientists who worked for the government, Willard Libby, John Goffman, and many others, were working to convince the public that they shouldn't worry. Of the multitude of scientists who served the government during that time, only a few ever came to oppose those

policies, and those who did were unable to keep their jobs or research grants. Gofman has become the leader in the movement to protect the public against radiation, especially, since 1971, through the Committee for Nuclear Responsibility.

Gofman has said: "I was stupid in those days. In 1955, '56, people like Linus Pauling were saying that the bomb fallout would cause all this trouble. I thought, 'We're not sure. If you're not sure, don't stand in the way of progress.' I could not have thought anything more stupid in my life."

"The big moment in my life happened while I was giving a health lecture to nuclear engineers. In the middle of my talk it hit me! What the hell am I saying? If you don't know whether low doses are safe or not, going ahead is exactly wrong. At that moment, I changed my position entirely."[17]

In 1979, Gofman said: "There is no way I can justify my failure to help sound an alarm over these activities many years sooner than I did. I feel that at least several hundred scientists trained in the biomedical aspect of atomic energy—myself definitely included—are candidates for Nuremburg-type trials for crimes against humanity for our gross negligence and irresponsibility. Now that we know the hazard of low-dose radiation, the crime is not experimentation—it's murder."[18, pp. 227–228]

Many ordinary people were making exactly that argument in the 1950s, but government censorship kept the most incriminating evidence from the public. The climate of intimidation spread throughout the culture, so that teachers who spoke about the dangers of radiation were called disloyal, and were fired. Now, people who don't want x-rays are treated as crackpots. Probably because of this cultural situation, Gofman's recommendations are very mild—simply for doctors to use good technology and to know what they are doing, which could lead to ten-fold or even hundred-fold dose reduction. Even with such mild restraint in the use of diagnostic x-rays, Gofman's well founded estimate is that 250,000 deaths caused by radiation could be prevented annually. I believe many more deaths would be prevented if ultrasound and MRI were used consistently instead of x-rays. Using Gofman's estimate, I think we can blame at least ten million deaths on just the medical x-rays that have been used inappropriately because of the policies of the U.S. government in the last half century. That wouldn't include the deaths caused by radioactive fallout from bomb tests and leaks from

nuclear power plants, or the vast numbers of people mentally impaired by all sorts of toxic radiation.

Although nearly all the people who committed the radiation crimes of the 1950s and 1960s have died or retired, the culture they created remains in the mass media and scientific journals, and in the medical and academic professions.

Medical journals describe ways to minimize diagnostic x-ray exposure, and they advocate many seemingly effective treatments for osteoporosis, giving an impression that progress is being made in "managing" osteoporosis, but the real situation is very different. Fractures resulting from osteoporosis are increasing, and osteoporosis is affecting younger and younger people. I think it would be reasonable to say that a woman with osteoporosis is usually better off when it's not diagnosed, because of the dangerous things prescribed for it. Estrogen has become the main "treatment" for osteoporosis, but many of the other ways of "managing" osteoporosis are both ineffective and unsafe.

Many women are told to stop taking a thyroid supplement when osteoporosis is diagnosed, but hypothyroidism often leads to hyperprolactinema and hypercortisolemia, which are two of the most clearly established causes of osteoporosis. Calcitonin, vitamin D-active metabolite, and estrogen-"HRT" treatments can cause respiratory alkalosis (relative hyperventilation),[19–24] and hypothyroidism produces a predisposition to hyperventilation.[25] Hyperventilation tends to cause calcium loss. In respiratory alkalolis, CO_2 (and sometimes bicarbonate) are decreased, impairing calcium retention, and in "metabolic alkalosis," with increased bicarbonate, calcium is retained more efficiently and bone formation is stimulated, and its dissolution is suppressed.

Other women are told to reduce their protein consumption, or to take fluoride or whatever drug has been most recently promoted. A protein deficiency is a clear cause of osteoporosis, and bone density corresponds to the amount of protein consumed. Milk protein, especially, protects against osteoporosis, independently of milk's other important nutrients. Too much fluoride clearly increases the risk of bone fractures,[26] and the side effects of other drugs haven't been properly studied in humans, while they often have dangerous effects in animals.

Calcium, magnesium, vitamin A, vitamin B_6, vitamin K, and vitamin D are important for the development and maintenance of bones. For example, a vitamin A deficiency limits the synthesis of progesterone and

proteins. In calcium deficiency, parathyroid hormone is increased, and tends to cause the typical changes of aging, shifting calcium from hard tissues to soft, and decreasing the ratio of extracellular to intracellular (excitatory) calcium.

Polyunsaturated fats are converted to prostaglandins (especially under the influence of estrogen), and several prostaglandins have toxic effects on bone. Those fats also suppress the formation of thyroid hormone and progesterone. The increased use of the unsaturated oils has coincided with the increase of osteoporosis.

The oxidation of proteins caused by free radicals is increased with aging and by the use of unsaturated fats, and it contributes to tissue atrophy, including the age-related shrinkage of the bones. In animal studies, "adequate" dietary protein, 13.8 % of the diet (equivalent to about 80 g/day for a person) is associated with more oxidative damage to tissue proteins than the very high protein diets, 25.7 % or 51.3 %, that would be equivalent to about 150 or 300 g of protein daily for a person.[27] Yet, many physicians recommend a low protein diet to protect against osteoporosis.

Avoiding fluoridated water and the polyunsaturated oils, and drinking two quarts of milk daily (which will provide only 66 g of protein), and using some other nutrient-rich foods such as eggs and fruits, are probably the basic things to protect the bones. For vitamins, especially K, occasional liver can be helpful. Meats, fruits, leaves, and coffee are rich in magnesium.

Some people have argued that the acidity of urine produced by eating meat causes calcium loss. However, a high protein diet also improves the absorption of calcium by the intestine. Another overlooked function of dietary protein is that it stimulates insulin secretion, and insulin is anabolic for bone.[28]

The same diet that protects against osteoporosis, i.e., plenty of protein and calcium, etc., also protects against kidney stones and other abnormal calcifications.

Breast Cancer

Ray Peat's Newsletter, 2006

It's important to know the realities of cancer in the population, the death rate from cancer, and the effects of its aggressive diagnosis and treatment. Appreciating those, I think the need for a new attitude toward cancer can be seen.

Official U.S. data for the years 1990 to 1993 showed 505,300 cancer deaths in 1990, and 529,900 cancer deaths in 1993. This was an increase of roughly 1.3 % per year (which was faster than the population growth) during the time in whichRodu and Cole[1] and agencies of the U.S. government claimed the death rate was decreasing one half percent (0.5 %) per year.

This increase happened despite the abnormal population bulge in the number of people between the ages of 35 and 50, resulting from the postwar baby boom. Cancer incidence is about ten times higher among the older population than in this younger age range, so in this abnormally structured population, the death rate from cancer is much lower than it would be if the population composition were the same as before the war, and it is lower than it will be in ten or twenty years, when the population bulge reaches the prime cancer years.

In 1994, total cancer deaths increased to 536,900 (an increase of 1.32 % over 1993). The crude death rate per 100,000 population was 203.2 in 1990, in 1993 it was 205.6, in 1994 it had increased to 206. This, despite the population distortion caused by the baby boom, causing a scarcity of people in the age groups with the highest rates of cancer mortality.

In the U.S. in 1994 there were altogether 2,286,000 deaths. In a population of about 260 million, this was a death rate of less than 1 % per year (about 0.88 %). The chance of dying that year for any person was less than one in a hundred. That doesn't mean that life expectancy is over 100 years, but that would be implied if we ignored the population bulge of the baby boomers, as the cancer statisticians are doing.

When the U.S. Department of Health and Human Services, and every major medical journal in the United States lies about the simple statistics of cancer death rates, it's clear that very powerful and dangerous social forces are operating.

Anyone who knows about the baby boom that started right after the second world war must also realize that in 1940, at the end of the great depression, when infant and childhood mortality was very high and people postponed having children, the population had a disproportionate number of old people, and that it would be outrageous to use the rate of cancer in the pre-war population to evaluate the rate of cancer in the post-war population. But that is what is being done, and the mass media are helping to prevent the public from questioning the official story about cancer.

If the health of the population in 1940 is to be compared to that of a very differently constituted later population, the appropriate method is to compare the rate of death among people of a certain age. The death rate from leukemia, especially among children, was greatly increased in the post-war years, when people were being exposed to radiation from atomic bomb tests. The death rates among adults of various ages, from breast cancer, prostate cancer, and melanoma have steadily increased. Rodu and Cole, who declared victory in the war against cancer, said the decline in total cancer mortality began in 1991.[1] If lung cancer is excluded, they say mortality from other cancers has been declining since 1950![2] The first time I saw this bizarre use of "age restandardization" was when Professor Bruce Ames was on a lecture tour for the American Cancer Society, and was speaking to the biology department at the University of Oregon. He showed a graph indicating that the mortality curves for most types of cancer in the U.S. had begun their downward curve in the late 1940s just after the A.C.S. came onto the scene. Even though I think the A.C.S. probably initiated the practice of age-standardizing with reference to the 1940 population, they don't always find that date suitable for their purposes. In fund-raising literature showing their past success in curing childhood leukemia, they restandardized mortality with reference to the postwar year when the leukemia death rate was at its highest, with the result that their cures appeared to be steadily lowering the death rate. But the incidence rate varied according to the intensity of the radioactive intensity that pregnant women were exposed to, and so both the incidence and the mortality fell after atmospheric testing was stopped.

Government officials, editors of the big medical journals, professors and broadcasters, have been able to get away with this huge statistical fraud. I suspect that they will soon feel encouraged to simply make up

the data that they want, because eventually "age standardization" isn't going to work to hide the actual increases in mortality. Since people with cancer usually die of something else, such as a stroke or heart failure, it will be no trick at all to make cancer mortality decline to be replaced by other causes of death. The precedent for such fabulizing of data exists in the FDA's approval of AZT, and other less notorious drugs.

Radiation, estrogen, and a variety of chemical pollutants are known to be the major causes of breast cancer, but the efforts of the cancer establishment have been directed toward denying that these avoidable agents are the cause of the great increase in breast cancer during the last several decades. The cancer industry, including major producers of chemotherapy drugs, subsidizes the American Cancer Society and "Breast Cancer Awareness Week," and it is in their interest to convince the public that early detection and conventional treatment with surgery, chemotherapy, and radiation are winning the war against cancer. There is always light at the end of the tunnel, in the war against cancer, just as there was in the Vietnam war. Their consistent effort to dissuade the government from acting to reduce the public's exposure to the known causes of cancer should make it clear that they are in the business of treating cancer, not eliminating it.

In the 1960s I read some articles in a small town newspaper about Leonell Strong's cancer research, and his treatment by the American Cancer Society and the Salk Institute. Leonell Strong had developed strains of mice for use in cancer research. In some of the strains, 100 % of the females developed mammary cancer. Strong had demonstrated that these strains had very high levels of estrogen. He showed me mice that he had treated with simple extracts of liver, that were free of cancer, and whose descendants remained free of cancer for several generations.

Strong had received his PhD in genetics under T. H. Morgan. For a person trained in classical genetics, and who had spent his career developing the supposedly genetically determined cancer trait, the elimination of the trait by a few injections must have been hard to understand, but at least he tried to understand it.

When he had earlier demonstrated the presence of a virus in the milk of cancer-prone mice, and when he showed the role of heredity in cancer, he was popular with the cancer business, but when he showed that "genetic" cancer could be eradicated with a simple treatment, he became the object of official abuse. He said that the Salk institute had

offered him a position to induce him to move with his large colony of mice from New York to San Diego, but when he arrived he found that he had no job, and his records of decades of research had been lost. He said that a memo which was discovered in a lawsuit revealed that the institute had just wanted his mice, and never intended to give him the promised job. For the cancer establishment, his discovery of a way to prevent cancer was not welcome.

In 1969, two years before the war against cancer had begun pouring public money into the pockets of the cancer establishment, Harry Rubin gave a lecture that criticized the cancer establishment's claim that it was curing cancer. He cited a study by a pathologist who had looked for cancer in the tissues of people who had been killed in accidents. He found identifiable cancers in the tissues of everyone over the age of fifty that he examined. If everyone over 50 has histologically detectable cancer, then the use of biopsy specimens as the basis for determining whether a person needs treatment has no scientific basis.

The definition of a disease, and the recognition of its presence, has an important place in medicine, but understanding its cause or causes is essential for both treatment and prevention. The dominant belief in medicine is that diseases are significantly caused by "genes," including diseases such as cancer, diabetes, psychoses, and neurological diseases. In Israel, ethnic groups that had never had much diabetes before immigrating, within a single generation had diabetes as often as other Israelis. Shortly after insulin became available for the treatment of diabetes, the incidence of the disease in the U.S. began to increase. The simple death rate from diabetes per 100,000 population is now higher than it was in 1920, before insulin treatment became available. Neurological diseases and autoimmune diseases, along with diabetes and cancer, have increased greatly in recent generations. These simply aren't genetic diseases, and there should be a shift of resources away from useless or harmful treatments toward their prevention.

Even when a disease's cause isn't clearly understood, it is essential to use logical thinking in diagnosing its presence. The presence of a certain gene or "genetic marker" is often thought to have great diagnostic significance, which it rarely has. But even gross "signs" of a disease can be used diagnostically only if we know that similar signs aren't present in perfectly healthy people. When pains are thought to be the result of a herniated intervertebral disk, x-ray pictures may be produced as

confirmation of the diagnosis. But when people without pains are just as likely to have herniated disks (about 2/3 of normal people have them), the diagnosis fails to be convincing. When x-rays or MRIs show "plaques" in the head, multiple sclerosis is often "confirmed," but when normal medical students show just as many brain plaques, the diagnosis must be questioned. Similarly, when mature people who were perfectly healthy until they were killed by an accident are found to always have identifiable cancers, any diagnosis of cancer that is based on a similar histological specimen must be reconsidered.

By diagnosing something that is as common and trivial as dandruff as "cancer," physicians can get a very high rate of cures, whether they use surgery, radiation, or chemotherapy. Abnormal cellular proliferation is usually harmless, but it has become an important part of a business that makes several billion dollars per year, with no definite benefits except the financial benefits for those in the business.

Before cancer treatment became culturally practically obligatory, and when fewer people died of cancer, some people lived into old age with clearly "malignant" cancers, and died of some other cause. The policy of leaving a cancer alone is now established for prostate cancer in old men. Until there is clear evidence to the contrary, a similar policy might be appropriate for many kinds of cancer.

If every year more people are treated for cancer, and every year more people die of cancer, one simply wonders whether fewer people would die if few were treated.

If the first rule of medicine is to do no harm, then the second rule, growing out of the first, would have to be to give no treatment without knowing what is being treated, and to have a valid basis for believing that the damage done by the treatment is not worse than the damage that the disease would cause. If cancer specialists haven't demonstrated that their treatments improve their patients' situation, then their professional activities aren't justified; the statistics suggest that they aren't.

There simply isn't a valid base of knowledge about the natural history of cancer development in humans to permit a valid judgment to be made about the meaning of particular signs or indicators or histological structures. The extensive use of mammograms has increased the diagnosis of "ductal carcinoma *in situ*" by more than 1000 % (a 16- or 18-fold increase in some hospitals, and expected to double in the next decade), increasing the number of mastectomies and other treatments, but the increased

treatments and early diagnosis haven't produced any visible change in the death rate.

The pathologists talk knowingly of "pre-neoplastic" conditions that indicate an increased risk of malignancy, but instead of data, what they have is an ideology about the nature of cancer. When they say that a growth pattern is premalignant or that a cell has a malignant structure, they might as well be talking about goblins, because the scientific basis for what they are saying is nothing but a belief in the ideology that cancer is "clonal," that a particular cancer derives from a single defective cell. They are so self-assured, and have so many sources to cite about the "clonal nature of cancer," that it seems impolite to suggest that they might simply be misusing language and logic.

Isn't a person derived from a single cell, and so, in that sense, "clonal"? As organs differentiate in the development of the organism, can't organs be traced back to the cells from which they developed? Isn't every tissue "a clone" in that sense? What is it that makes the "clonal" nature of cancer tissue so special? Isn't it just that a nasty, mean, malignant tissue is, mentally, traced back to a "malignant" cell, by analogy with the way good tissues are traced back to good cells? If the tumor is odious, it must derive from an odious cell, and what could make that cell so hateful if it is genetically identical to the good cells? Therefore, the goblin reasoning goes, a genetic mutation must have produced the evil cell.

The actual evidence is that there are broad changes in tissues preceding the appearance of cancer. The goblin theory explains this by saying that a multitude of "precancerous" mutations occurred before the mutant cancer cell appeared. Harry Rubin has carefully shown experimentally and logically that cancer precedes the genetic changes that occur in tumors. But the ideology that cancer is the result of a genetic mutation forces its devotees to say that the genetic changes that can be found in a mature tumor must have occurred in one cell that was previously not malignant. An effect is identified as a cause.

The clonal-goblin theory of cancer leads logically to the conclusion that the cancer clone must be exorcised by surgery, chemotherapy, and/or radiation.

The biological theory of cancer, on the other hand, is inclined to view the normal and abnormal development of cells in terms of the cells' responses to conditions.

Estrogen and ionizing radiation are the most clearly documented causes of breast cancer. Their excitatory effects lead to inflammation, edema, fibrosis, and interruption of intercellular regulatory processes. Radiation is estrogenic, and increased estrogenic stimulation produces growth and temporary loss of differentiated functions. Estrogen and radiation aren't the only things that can cause these systematic changes in the structure of tissues—for example, vitamin A deficiencies, hypothyroidism, chlorinated hydrocarbons, irritation, and lack of oxygen can cause similar changes—but estrogen and irradiation have been studied enough to give us a fairly distinct picture of the real processes involved in the development of cancer.

Polyunsaturated fats are another clearly identified cause of cancer, especially breast cancer. These fats synergize with estrogen, and sensitize to radiation. Their effects on the mother can be seen in the offspring, as an increased tendency to develop breast or prostate cancer.

An individual's hormone balance can be disrupted by exposure to radiation, estrogens, or unsaturated fats. The hormonal balance of the parent is imprinted upon the offspring, acting on the chromosomes, the liver, brain, genitals, pituitary, bones—in fact, the prenatal imprint can probably be found everywhere in the offspring.

It's easy to reduce our exposure to radiation, by avoiding mammograms, bone density scans, and other x-rays of all sorts. Ultrasound and MRI can produce good images of any tissue without the deadly effects of ionizing radiation.

Polyunsaturated fats can be reduced by careful selection of foods, but the food industry is finding ways to contaminate traditionally safe foods, such as beef and milk, by using new kinds of animal feed. Still, milk, cheese, beef, and lamb are safe, considering their high nutritional content, and the remarkable purification that occurs in the rumen of cows, sheep, and goats. Some studies suggest a protective effect from saturated fat.[3]

Estrogenic influences can be significantly reduced by avoiding foods such as soy products and unsaturated fats, by eating enough protein to optimize the liver's elimination of estrogen, and by using things such as bulk-forming foods (raw carrots, potatoes, and milk, for example) that stimulate bowel action and prevent reabsorption of estrogens from the intestine. Avoiding hypothyroidism is essential for preventing chronic retention or formation of too much estrogen.

Some studies show that dietary starch, rather than fat, is associated with breast cancer. Starch strongly stimulates insulin secretion, and insulin stimulates the formation of estrogen.

Estrogen is formed in fat cells under the influence of cortisol, and this formation is suppressed by progesterone and thyroid. Postmenopausal obesity is associated with increased estrogen and breast cancer. The prevention of weight gain, and supplementation with thyroid and progesterone if necessary, should be protective against many types of cancer, especially breast, kidney, and uterine cancer.

Prenatal or early life exposure to estrogens, including phytoestrogens, or to irradiation, or to polyunsaturated oils, increases the incidence of mammary cancers in adulthood.

Protein deficiency prenatally or early in life causes a life-long excess of serotonin. Feeding an excess of tryptophan, the precursor of serotonin, during pregnancy produces pituitary and mammary tumors in the offspring. Serotonin, besides being closely associated with the effects of estrogen (e.g., mediating its stimulation of prolactin secretion) and polyunsaturated fats, can be metabolized into carcinogens.

Prenatal protein deficiency and excess unsaturated oils predispose to a developmental pattern involving hypothyroidism and hyperestrogenism; puberty occurs at an earlier age, along with a tendency to gain weight. Inflammatory processes (e.g., "autoimmune diseases") are usually intensified under those conditions. Inflammation itself increases the effects of estrogen and serotonin.

Both preventively and therapeutically, the use of the antiinflammatory and antioxidative substances such as aspirin, caffeine, progesterone, and thyroid hormone would seem appropriate. Aspirin is coming to be widely accepted as an anticancer agent, and at moderate doses can cause cancer cells to die. It, like progesterone and thyroid, has a wide variety of anti-estrogenic effects. Especially when a tumor is painfully inflamed, aspirin's effects can be quick and dramatic. However, people aren't likely to be pleased if their cancer doctor tells them to "take aspirin and call me in six months." Aspirin's reputation for causing stomach bleeding causes people to avoid it, even when the alternative is something that's seriously toxic to other organs, and it might just seem too ordinary to be considered as a powerful anticancer drug.

Because of the toxic (carcinogenic, and anti-respiratory) effects of the "essential fatty acids," which are usually stored in the tissues in very

large quantities, it's important to avoid the stresses or hunger that would release the fats into the blood stream. Estrogens and adrenalin and serotonin and growth hormone, and prolonged darkness, increase the release of the free fatty acids. Frequent meals, including some saturated fats such as coconut oil, and a balance of protein, sugars, and salts, will minimize the release of stored fats.

The population trends toward greater obesity and earlier puberty, both of which are associated with a higher risk of breast cancer, suggest that the war against cancer is far from over. In the 19th century when the incidence of breast cancer was much lower than it is now, puberty usually occurred around the age of 17. In countries with a low incidence of breast cancer, puberty still occurs in the middle to late teens. People who are now 100 generally had puberty years later than girls do now. The biological changes now seen in children in the U.S. suggest that the incidence of degenerative diseases of all sorts is likely to increase as these children grow up.

A metabolic approach to the prevention and treatment of cancer would have many beneficial side effects, such as producing generally healthier, happier and brighter babies.

Caffeine: A Vitamin-Like Nutrient, or Adaptogen

Questions About Tea and Coffee, Cancer and Other Degenerative Diseases, and the Hormones

Ray Peat's Newsletter, 2006

THERE is a popular health-culture that circulates mistaken ideas about nutrition, and coffee drinking has been a perennial target of this culture. It is commonly said that coffee is a drug, not a food, and that its drug action is harmful, and that this harm is not compensated by any nutritional benefit. Most physicians subscribe to most of these "common sense" ideas about coffee, and form an authoritative barrier against the assimilation of scientific information about coffee.

One definition of a vitamin is that it is an organic chemical found in foods, the lack of which causes a specific disease, or group of diseases. A variety of substances that have been proposed to be vitamins haven't been recognized as being essential, and some substances that aren't essential are sometimes called vitamins. Sometimes these issues haven't had enough scientific investigation, but often nonscientific forces regulate nutritional ideas.

The definition of "a disease" isn't as clear as text-book writers have implied, and "causality" in biology is always more complex than we like to believe.

Nutrition is one of the most important sciences, and should certainly be as prestigious and well financed as astrophysics and nuclear physics, but while people say "it doesn't take a brain surgeon to figure that out," no one says "it doesn't take a nutritionist to understand that." Partly, that's because medicine treated scientific nutrition as an illegitimate step-child, and refused throughout the 20th century to recognize that it is a central part of scientific health care. In the 1970s, physicians and dietitians were still ridiculing the idea that vitamin E could prevent or cure diseases of the circulatory system, and babies as well as older people were given "total intravenous nutrition" which lacked nutrients that are essential to life, growth, immunity, and healing. Medicine and science are powerfully institutionalized, but no institution or profession has existed for the purpose of encouraging people to act reasonably.

In this environment, most people have felt that subtleties of definition, logic and evidence weren't important for nutrition, and a great

amount of energy has gone into deciding whether there were "four food groups" or "seven food groups" or a "nutritional pyramid." The motives behind governmental and quasi-governmental nutrition policies usually represent something besides a simple scientific concern for good health, as when health care institutions say that Mexican babies should begin eating beans when they reach the age of six months, or that non-whites don't need milk after they are weaned. In a culture that discourages prolonged breast feeding, the effects of these doctrines can be serious.

After a century of scientific nutrition, public nutritional policies are doing approximately as much harm as good, and they are getting worse faster than they are getting better.

In this culture, what we desperately need is a recognition of the complexity of life, and of the political-ecological situation we find ourselves in. Any thinking which isn't "system thinking" should be treated with caution, and most contemporary thinking about health neglects to consider relevant parts of the problem-system. "Official" recommendations about salt, cholesterol, iron, unsaturated and saturated fats, and soybeans have generally been inappropriate, unscientific, and strongly motivated by business interests rather than by biological knowledge.

Definitions have rarely distinguished clearly between nutrients and drugs, and new commercial motives are helping to further blur the distinctions.

Essential nutrients, defensive (detoxifying, antistress) nutrients, hormone-modulating nutrients, self-actualization nutrients, growth regulating nutrients, structure modifiers, life extension agents, transgenerationally active (imprinting) nutrients—the line between nutrients and biological modifiers often depends on the situation. Vitamins D and A clearly have hormone-like properties, and vitamin E's effects, and those of many terpenoids and steroids and bioflavonoids found in foods, include hormone-like actions as well as antioxidant and pro-oxidant functions. The concept of "adaptogen" can include things that act like both drugs and nutrients.

Some studies have suggested that trace amounts of nutrients could be passed on for a few generations, but the evidence now indicates that these transgenerational effects are caused by phenomena such as "imprinting." But the hereditary effects of nutrients are so complex that their recognition would force nutrition to be recognized as one of the

most complex sciences, interwoven with the complexities of growth and development.

The idea that poor nutrition stunts growth has led to the idea that good nutrition can be defined in terms of the rate of growth and the size ultimately reached. In medicine, it is common to refer to an obese specimen as "well nourished," as if quantity of food and quantity of tissue were necessarily good things. But poisons can stimulate growth ("hormesis"), and food restriction can extend longevity. We still have to determine basic things such as the optimal rate of growth, and the optimal size.

Nutrition textbooks flatly describe caffeine as a drug, not a nutrient, as if it were obvious that nutrients can't be drugs. Any of the essential nutrients, if used in isolation, can be used as a drug, for a specific effect on the organism that it wouldn't normally have when eaten as a component of ordinary food. And natural foods contain thousands of chemicals, other than the essential nutrients. Many of these are called nonessential nutrients, but their importance is being recognized increasingly. The truth is that we aren't sure what they "aren't essential" for. Until we have more definite knowledge about the organism I don't think we should categorize things so absolutely as drugs or nutrients.

The bad effects ascribed to coffee usually involve administering large doses in a short period of time. While caffeine is commonly said to raise blood pressure, this effect is slight, and may not occur during the normal use of coffee. Experimenters typically ignore essential factors. Drinking plain water can cause an extreme rise in blood pressure, especially in old people, and eating a meal (containing carbohydrate) lowers blood pressure. The increased metabolic rate caffeine produces increases the cellular consumption of glucose, so experiments that study the effects of coffee taken on an empty stomach are measuring the effects of increased temperature and metabolic rate, combined with increased adrenaline (resulting from the decrease of glucose), and so confuse the issue of caffeine's intrinsic effects.

In one study,[1] the drugs were introduced directly into the carotid artery to study the effects on the blood vessels in the brain. Caffeine increased the blood volume in the brain, while decreasing the resistance of the vessels, and this effect is what would be expected from its stimulation of brain metabolism and the consequent increase in carbon dioxide, which dilates blood vessels.

In the whole body, increased carbon dioxide also decreases vascular resistance, and this allows circulation to increase, while the heart's work is decreased, relative to the amount of blood pumped. But when the whole body's metabolism is increased, adequate nutrition is crucial.

In animal experiments that have been used to argue that pregnant women shouldn't drink coffee, large doses of caffeine given to pregnant animals retarded the growth of the fetuses. But simply giving more sucrose prevented the growth retardation. Since caffeine tends to correct some of the metabolic problems that could interfere with pregnancy, it is possible that rationally constructed experiments could show benefits to the fetus from the mother's use of coffee, for example by lowering bilirubin and serotonin, preventing hypoglycemia, increasing uterine perfusion and progesterone synthesis, synergizing with thyroid and cortisol to promote lung maturation, and providing additional nutrients.

One of the most popular misconceptions about caffeine is that it causes fibrocystic breast disease. Several groups demonstrated pretty clearly that it doesn't, but there was no reason that they should have had to bother, except for an amazingly incompetent, but highly publicized, series of articles—classics of their kind—by J. P. Minton, of Ohio State University. Minton neglected to notice that the healthy breast contains a high percentage of fat, and that the inflamed and diseased breast has an increased proportion of glandular material Fat cells have a low level of cyclic AMP, a regulatory substance that is associated with normal cellular differentiation and function, and is involved in mediating caffeine's ability to inhibit cancer cell multiplication. Minton argued that cAMP increases progressively with the degree of breast disease, up to cancer, and that cAMP is increased by caffeine. A variety of substances other than caffeine that inhibit the growth of cancer cells (as well as normal breast cells) act by increasing the amount of cyclic AMP, while estrogen lowers the amount of cAMP and increases cell growth. Minton's argument should have been to use more caffeine, in proportion to the degree of breast disease, if he were arguing logically from his evidence. Caffeine's effect on the breast resembles that of progesterone, opposing estrogen's effects.

Many studies over the last 30 years have shown caffeine to be highly protective against all kinds of carcinogenesis, including estrogen's carcinogenic effects on the breast. Caffeine is now being used along with some of the standard cancer treatments, to improve their effects or

to reduce their side effects. There are substances in the coffee berry besides caffeine that protect against mutations and cancer, and that have shown strong therapeutic effects against cancer. Although many plant substances are protective against mutations and cancer, I don't know of any that is as free of side effects as coffee.

To talk about caffeine, it's necessary to talk about uric acid. Uric acid, synthesized in the body, is both a stimulant and a very important antioxidant, and its structure is very similar to that of caffeine. A deficiency of uric acid is a serious problem. Caffeine and uric acid are in the group of chemicals called purines.

Purines (along with pyrimidines) are components of the nucleic acids, DNA and RNA, but they have many other functions. In general, substances related to purines are stimulants, and substances related to pyrimidines are sedatives.

When the basic purine structure is oxidized, it becomes in turn hypoxanthine, xanthine, and uric acid, by the addition of oxygen atoms. When methyl groups (CH_3) are added to nitrogens in the purine ring, the molecule becomes less water soluble. Xanthine (an intermediate in purine metabolism) has two oxygen atoms, and when three methyl groups are added, it becomes trimethyl xanthine, or caffeine. With two methyl groups, it is theophylline, which is named for its presence in tea. We have enzyme systems which can add and subtract methyl groups; for example, when babies are given theophylline, they can convert it into caffeine.

We have enzymes that can modify all of the methyl groups and oxygen atoms of caffeine and the other purine derivatives. Caffeine is usually excreted in a modified form, for example as a methylated uric acid.

One of the ways in which uric acid functions as an "antioxidant" is by modifying the activity of the enzyme xanthine oxidase, which in stress can become a dangerous source of free radicals. Caffeine also restrains this enzyme. There are several other ways in which uric acid and caffeine (and a variety of intermediate xanthines) protect against oxidative damage. Coffee drinkers, for example, have been found to have lower levels of cadmium in their kidneys than people who don't use coffee, and coffee is known to inhibit the absorption of iron by the intestine, helping to prevent iron overload.

Toxins and stressors often kill cells, for example in the brain, liver, and immune system, by causing the cells to expend energy faster than it can be replaced. There is an enzyme system that repairs genetic damage, called "PARP." The activation of this enzyme is a major energy drain, and substances that inhibit it can prevent the death of the cell. Niacin and caffeine can inhibit this enzyme sufficiently to prevent this characteristic kind of cell death, without preventing the normal cellular turnover; that is, they don't produce tumors by preventing the death of cells that aren't needed.

The purines are important in a great variety of regulatory processes, and caffeine fits into this complex system in other ways that are often protective against stress. For example, it has been proposed that tea can protect against circulatory disease by preventing abnormal clotting, and the mechanism seems to be that caffeine (or theophylline) tends to restrain stress-induced platelet aggregation.

When platelets clump, they release various factors that contribute to the development of a clot. Serotonin is one of these, and is released by other kinds of cell, including mast cells and basophils and nerve cells. Serotonin produces vascular spasms and increased blood pressure, blood vessel leakiness and inflammation, and the release of many other stress mediators. Caffeine, besides inhibiting the platelet aggregation, also tends to inhibit the release of serotonin, or to promote its uptake and binding.

[2], found that high uric acid levels seem to protect against the development of Parkinson's disease. They ascribed this effect to uric acid's antioxidant function. Coffee drinking, which lowers uric acid levels, nevertheless appeared to be much more strongly protective against Parkinson's disease than uric acid.

Possibly more important than coffee's ability to protect the health is the way it does it. The studies that have tried to gather evidence to show that coffee is harmful, and found the opposite, have provided insight into several diseases. For example, coffee's effects on serotonin are very similar to carbon dioxide's, and the thyroid hormone's. Noticing that coffee drinking is associated with a low incidence of Parkinson's disease could focus attention on the ways that thyroid and carbon dioxide and serotonin, estrogen, mast cells, histamine and blood clotting interact to produce nerve cell death.

Thinking about how caffeine can be beneficial across such a broad spectrum of problems can give us a perspective on the similarities of their underlying physiology and biochemistry, expanding the implications of stress, biological energy, and adaptability.

The observation that coffee drinkers have a low incidence of suicide, for example, might be physiologically related to the large increase in suicide rate among people who use the newer antidepressants called "serotonin reuptake inhibitors." Serotonin excess causes several of the features of depression, such as learned helplessness and reduced metabolic rate, while coffee stimulates the uptake (inactivation or storage) of serotonin, increases metabolic energy, and tends to improve mood. In animal studies, it reverses the state of helplessness or despair, often more effectively than so-called antidepressants.

The research on caffeine's effects on blood pressure, and on the use of fuel by the more actively metabolizing cells, hasn't clarified its effects on respiration and nutrition, but some of these experiments confirm things that coffee drinkers usually learn for themselves.

Often, a woman who thinks that she has symptoms of hypoglycemia says that drinking even the smallest amount of coffee makes her anxious and shaky. Sometimes, I have suggested that they try drinking about two ounces of coffee with cream or milk along with a meal. It's common for them to find that this reduces their symptoms of hypoglycemia, and allows them to be symptom-free between meals. Although we don't know exactly why caffeine improves an athlete's endurance, I think the same processes are involved when coffee increases a person's "endurance" in ordinary activities.

Caffeine has remarkable parallels to thyroid and progesterone, and the use of coffee or tea can help to maintain their production, or compensate for their deficiency. Women spontaneously drink more coffee premenstrually, and since caffeine is known to increase the concentration of progesterone in the blood and in the brain, this is obviously a spontaneous and rational form of self-medication, though medical editors like to see things causally reversed, and blame the coffee drinking for the symptoms it is actually alleviating. Some women have noticed that the effect of a progesterone supplement is stronger when they take it with coffee. This is similar to the synergy between thyroid and progesterone, which is probably involved, since caffeine tends to locally activate thyroid secretion by a variety of mechanisms, increasing cyclic

AMP and decreasing serotonin in thyroid cells, for example, and also by lowering the systemic stress mediators.

Medical editors like to publish articles that reinforce important prejudices, even if, scientifically, they are trash. The momentum of a bad idea can probably be measured by the tons of glossy paper that have gone into its development. Just for the sake of the environment, it would be nice if editors would try to think in terms of evidence and biological mechanisms, rather than stereotypes.

Calcium and Disease

Hypertension, Organ Calcification, & Shock, vs. Respiratory Energy

Ray Peat's Newsletter, 2009

ALMOST all biologists think of the organism as a machine, regulated by information according to innate programs. When it comes down to the details, their explanations sometimes make Rube Goldbergs imaginary contraptions seem elegant. At their best, they usually rely on some mysterious things called ionic pumps, that perform active transport, powered by little motors, under instructions from molecules that act on their specific receptors. When things get unmanageable, the biologists speak of paradoxes.

Calcium is the most studied of all regulatory molecules, so it isn't surprising that there is more than one calcium paradox. But there are ways of looking at the organism, focusing on energy metabolism, that don't involve the *ad hoc* theory of calcium pumps, and that make it easy to keep things in context.

Ionized atoms and molecules behave in orderly ways, in relation to their size and their electrical charge. Organic material, even when it's dead, selectively binds certain metal ions, and excludes others. The living organism produces a stream of metabolic products, such as carbon dioxide or lactic acid, which interact specifically with each other and with the metal ions, modifying their concentrations inside cells and in the body fluids. This movement of ions can be called active transport, without invoking the mysterious machinery of membrane pumps. Chemical changes produced inside cells, for example by respiration, create different electrical charges in different compartments (inside and

> "It is extremely important to realize that calcium deposits in soft tissues become worse when the diet is low in calcium. Persons suffering from arthritis, bursitis, scleroderma, hardening of the arteries and any abnormality where calcium deposits or spurs may cause pain are often afraid to eat foods rich in calcium. Actually they can never improve until their calcium and magnesium intakes are adequate. Not infrequently physicians tell individuals with kidney stones to avoid all milk, thereby causing stones to form even more rapidly. Such calcium deposits can also occur when vitamin E is undersupplied. After open-heart surgery, when both magnesium and vitamin E are drastically needed and could easily be given, the calcification of heart muscles often becomes so severe that it can cause death within a few days."[1, p. 171–172]

outside of capillaries, for example) which affect the movements of water and ions, by simple physical processes, not by molecular pumps.

The result of these passive and active processes is that each kind of ion has a characteristic concentration in each compartment, according to the metabolic energy state of the organism.

Magnesium and potassium are mainly intracellular ions, sodium and calcium are mainly extracellular ions. When cells are excited, stressed, or de-energized, they lose magnesium and potassium, and take up sodium and calcium. The mitochondria can bind a certain amount of calcium during stress, but accumulating calcium can reach a point at which it inactivates the mitochondria, forcing cells to increase their inefficient glycolytic energy production, producing an excess of lactic acid. Abnormal calcification begins in the mitochondria.

When cells are stressed or dying, they take up calcium, which tends to excite the cells at the same time that it inhibits their energy production, intensifying their stress. A cramp or a seizure is an example of uncontrolled cellular excitation. Prolonged excitation and stress contribute to tissue inflammation and fibrosis.

Gross calcification generally follows the fibrosis that is produced by inflammation.

Arteries, kidneys, and other organs calcify during aging. At the age of 90, the amount of calcium in the elastic layer of an artery is about 35 times greater than at the age of 20. Nearly every type of tissue, including the brain, is susceptible to the inflammatory process that leads through fibrosis to calcification. The exception is the skeleton, which loses its calcium as the soft tissues absorb calcium.

These observations lead to some simplifying ideas about the nature of aging and disease.

Some people who know about the involvement of calcium in aging, stress, and degeneration suggest eating a low calcium diet, but since we all have skeletons, dietary calcium restriction can't protect our cells, and in fact, it usually intensifies the process of calcification of the soft tissues. Statistics from several countries have clearly shown that the mortality rate (especially from arteriosclerotic heart disease, but also from some other diseases, including cancer) is lower than average in regions that have hard water, which often contains a very large amount of either calcium or magnesium.

Many studies have shown that dietary calcium (or vitamin D, which increases calcium absorption) can have very important antiinflammatory effects.

About 25 years ago, David McCarron noticed that the governments data on diet and hypertension showed that the people who ate the most salt had the lowest blood pressure, and those who ate the least salt had the highest pressure. He showed that a calcium deficiency, rather than a sodium excess, was the most likely nutritional explanation for hypertension.

Hans Selye found that some steroids contribute to inflammation and calcification. Animals could be sensitized to develop calciphylaxis, an intense, localized interaction of inflammation and calcification.

In the 1970s, Constance Martin pointed out that, up to that time, estrogen was known to increase soft tissue calcium, but hadn't been shown to improve bone calcification and strength.

Oxygen deprivation, cyanide poisoning, x-irradiation, and all other sorts of injury also increase the calcium content of soft tissues.

One of Selyes colleagues, G. Jasmin, showed that magnesium deficiency causes inflammation. A deficiency of either calcium or magnesium can stimulate the parathyroid glands to produce more hormone (parathyroid hormone, PTH), which increases calcium absorption, but also removes calcium from the bones. This hormone, responding to a dietary calcium or magnesium deficiency, is an important factor in causing cells to take up too much calcium, and its excess is associated with many inflammatory and degenerative diseases.

Interleukin-6 (IL-6), an inflammatory cytokine which increases with aging, is commonly considered to have an important role in the multiple processes of atrophy in old age. One of the things which can increase the production of IL-6 is the parathyroid hormone (PTH), which increases the amount of calcium circulating in the blood, partly by causing it to be removed from the bones; IL-6 stimulates the process of calcium removal from bones.

Some of the interactions of hormones and other regulatory chemicals are interesting, even though they are normally treated as if they were parts of a machine that operates according to a hidden program written in the genes. Prolactin, which is increased under the influence of estrogen or serotonin, causes the body to lose calcium (drawing it from the bones), and it stimulates the secretion of PTH, which compensates for the cal-

cium loss by increasing its mobilization from bones. Prolactins action on bone is at least partly by increasing IL-6 formation; IL-6 stimulates the release of prolactin. Serotonin and IL-6 stimulate each others secretion, and PTH and serotonin each stimulate the others release.

PTH (like estrogen and serotonin) inhibits cellular respiration and activates glycolysis, lowering the ATP level and shifting the cells metabolism toward the production of lactic acid rather than carbon dioxide. PTH also causes bicarbonate to be lost in the urine.

Since the formation of carbon dioxide lowers the intracellular pH, and the formation of lactic acid raises it (through the reaction of NADH with pyruvate), the proteins in the cell become more strongly negatively charged under the influence of oxygen deprivation, or under the influence of these hormones. In the cell with high pH and increased negative electrical charge, the positively charged calcium ion is absorbed into the cytoplasm. The calcium can enter from the relatively concentrated external fluid, but it can also be released from acidic intracellular stores, the way serotonin is released by a disturbance of pH.

There are several other pro-inflammatory substances, such as the cytokines, that have a similar effect on cellular energy systems.

The antimetabolic actions of PTH mimic those seen in aging and diabetes, and surgical removal of the parathyroid glands has been known to eliminate diabetes. PTH can cause diuresis, leading to loss of blood volume and dehydration, hypertension, paralysis, increased rate of cell division, and growth of cartilage, bone, and other tissues.

Simply eating an adequate amount of calcium and magnesium can alleviate many problems related to stress and aging that are considered serious, such as heart arrhythmia, pancreatitis, and tissue calcification. The antiinflammatory, anti-allergy actions of calcium and magnesium are well established, and there is clear evidence that obesity and various emotional disturbances can result from their deficiency. Chronically high PTH can produce anemia, by a variety of mechanisms.

Since a very low sodium diet increases the loss of magnesium, by increasing aldosterone synthesis, simply increasing the amount of sodium in the diet can help some people to balance their minerals and minimize stress. During fasting and other intense stress, the kidneys destroy a large amount of protein to form ammonia to maintain their ability to excrete acids, so using a large amount of the alkaline minerals can reduce the protein catabolism.

A diet of milk and fruit, or milk and meat, provides a nutritional balance with generous amounts of calcium and magnesium. Leafy vegetables are a very rich source of magnesium, but they are also a potential source of large amounts of lead and other toxins. In 1960, many people, including the U.S.government, were advocating the use of a largely vegetarian diet for children, because of the amount of radioactive strontium in milk. I compared the amount of strontium in a diet of vegetables that would provide the necessary quantity of calcium and protein, and it was clear that vegetables were the worst source of radioactive strontium, because their ratio of strontium to calcium was much higher than the ratio in milk. The cows were concentrating calcium and protein from the contaminated plant foods, eliminating much of the strontium. This principle still applies to the toxins that are currently found in the U.S. food supply.

Milk has many protective effects besides providing calcium.

Many babies are being given milk substitutes (health food drinks) made from soy or rice, with terrible consequences. The same products used by adults have less disastrous effects in the short term, but are still likely to contribute to degeneration and dementia.

Much of the intracellular magnesium is complexed with ATP, and helps to stabilize that molecule. If cellular energy production is low, as in hypothyroidism, cells tend to lose their magnesium very easily, shifting the balance toward the lower energy molecule, ADP, with the release of phosphate. ADP complexes with calcium, rather than magnesium, increasing the cells calcium content.

Increased intracellular calcium, in association with excess nitric oxide and excitatory amino acids, is involved in several neurodegenerative diseases, including ALS, Alzheimers disease, Parkinsons disease, Huntingtons chorea, and epilepsy. Magnesium, nicotine, progesterone, and many other substances are known to protect against excitotoxic calcium overload, but there is no coherent effort in the health professions to make rational use of the available knowledge.

Respiration and carbon dioxide are the basic antagonists of the PTH. At birth, a baby has practically no PTH, probably because of the high intrauterine concentration of carbon dioxide, but within a few days the PTH rises.

Increased carbon dioxide favors bone formation, and decreased bicarbonate favors the loss of calcium from bone.[2,3] The use of sodium bicarbonate can stimulate bone formation.

A low protein diet, similar to that eaten by a large proportion of women (0.8 g/kg of body weight) increases PTH, and so probably contributes to the development of osteoporosis and the diseases of calcification. In an extreme protein deficiency, there is a shift towards inflammation, serotonin excess, and excessive clotting, which might be related to the effect of the milder, more common protein deficiency. Many people advocate a low protein diet, specifically to prevent or treat osteoporosis, but the cultures that traditionally have had extremely high protein diets, such as the Masai, are very healthy. Recent studies[4] are emphasizing the importance of animal protein in preventing osteoporosis.

Traditional meat-eating cultures efficiently use the whole animal, including blood, skin, bones, and the various organs, rather than just the muscles. That diet is favorable for calcium regulation, because it provides more vitamin A, D, E, and K, calcium, and gelatin, and less of the pro-inflammatory amino acids, tryptophan and cysteine.

Most loss of calcium from bones occurs during the night. PTH tends to cycle with prolactin, which increases during the night, along with cortisol and the other stress hormones. These nocturnal hormones probably account for the morning stiffness seen in many rheumatic conditions, connective tissue diseases, and in aging.

Progesterone, which increases the carbon dioxide content of the tissues, is remarkably able to inhibit the actions of most of the inflammatory and catabolic mediators, and to protect against degenerative calcification and osteoporosis. It also protects against abnormal clotting. PTH increases platelet calcium concentration, and under some conditions can produce inappropriate coagulation.

Aspirin inhibits the actions of PTH, helping to prevent the calcification of inflamed tissues, and it inhibits the loss of calcium from bones. Aspirin decreases the release of IL-6.

A protein called the PTH-related protein (PTHrP) has the same functions as PTH, but can be produced in any tissue. It is responsible for the hypercalcemia of cancer, and is apparently involved in the frequent metastasis of breast cancer to the bones.

With only a small change in the theory of the nature of a living organism, recognizing the importance of the interactions of metabo-

lites and structural substances, controlled by energetic metabolism, real progress could be made in understanding disease and health. The most important calcium paradox is that medical journals (e.g., International J. of Cardiology, Dec., 2002) are still promoting the idea that eating too much calcium causes hardening of the arteries and other diseases of calcification.

Can Art Instruct Science?

William Blake as a Biological Visionary

Ray Peat's Newsletter, 2006

WHEN I started studying William Blake in the 1950s, it seemed that only English majors knew who he was, but today, I think more people might recognize The Tyger as Blake's than would be able to identify poems by Keats, Byron, Shelley, or Wordsworth. After 200 years, his writing seems contemporary, while other poets' works have become dated, and are valued mostly as cultural background. But I don't think this means that his work is any easier to understand than it was when he wrote it. It means that other poets tied their writing to frameworks which have receded into the background, while Blake's words were chosen in a way that allowed them to travel across the centuries without loss. Even though such universality is a goal of science as well as of art, most of what passed for science in the 18th century is today of only historical interest.

Everywhere in our culture, authoritarian ignorance has disproportionate influence. Most of the published work in our culture treats the succession of authoritarian academic/scientific/political cults as if this were simply the way history and human nature work, and must work. But this mechanical historical process is only superficial, and below this surface, individuals and groups have always lived as though time behaved very differently for them. William Blake was a person who investigated this discrepancy between official cultural progression, and real human possibility, and his ideas might be able to do essentially what he suggested they could do: Provide a way to by-pass the officially established mechanistic view of reality, into a more fully human reality. Since Blake ridiculed established doctrines in medicine, chemistry, mathematics, and Newtonian physics, many people have dismissed him as a religious nut, but the way in which he criticized them indicates that he simply believed that they were bad science; he also criticized conventional art and morality, because he believed that they were destroying art and morality.

A group that was active in the 1950s, called Synectics, developed several mental procedures that they found to be useful in teaching people to solve problems creatively. These included ways to improve thinking

by analogy, to get people out of the ruts of conventional thinking. Personification, fantasy, biological imagery, "making the familiar strange," they found, seemed to tap into natural biological and mental processes to increase the ability to direct energy toward valid solutions to practical or artistic problems. They found that experts had to overcome their special knowledge before they could usefully solve problems in "their field," and they showed that much of the mystery could be removed from the creative process. Simply putting aside dogmatic mental frameworks was crucial.

When you believe that you have adequate, expert knowledge, a passive, logical, deductive form of mental activity seems appropriate. Deduction always goes from a higher level of generality to a lower level of generality. Mental passivity therefore is likely to be associated with the belief that we have the decisive knowledge already stored in memory. If we believe that we create higher degrees of generality, as appropriate solutions to novel problems, then we are committed to an active mental life. Perception, combined with the discovery and invention of new patterns in the world, will be actively oriented toward the future, while the deductive, merely analytical, manner of thought will be tied to the past.

Blake's work, I think, is of continued and increased interest because he discovered something of great importance, namely, how to avoid dogmatisms of all sorts. Many students who are assigned to write about a poem of Blake's are puzzled, and ask what it means. When they find out that they understand the words and the syntax, it turns out that the only problem was that they were taught that they had to "interpret" poetry. And that they don't think he could have meant what he said. Most twentieth century students are too stodgy to accept Blake's writing easily. In the 1950s, some people couldn't understand Alan Ginsberg's poetry, because they didn't think anyone was allowed to say such things. That is the kind of problem students have with Blake.

But it's not just high school and college students who can't believe that Blake meant what he said. I recently reviewed the comments on The Tyger that have been published in the forty years since I wrote my MA thesis on Blake, and it seems that these academic experts are having the same kind of problem. Dostoyevsky wrote about this problem in The Double—it is the problem of self-assertion, of seeing oneself reflected everywhere in the world. In Dostoyevsky's story, Dream of an Odd

Fellow, the theme is stated even more clearly—the world is very boring, and everything seems the same as everything else, until you can escape from a certain interpretive framework, to see what is really present to you. In Blake's phrase, if the many become the same as the few when possessed, "more, more," is the cry of a mistaken soul; Blake said, over and over, that the many do not become the same as the few, that we are always moving into a new world as we learn more, except when we find ourselves in the mental manacles of interpretation.

It's easy to forget how pervasive philosophical interpretation is in everyday life and in the so-called sciences, and how much the sciences owe to long-standing theological commitments. Within the last generation, many influential people have said that facts don't matter (and I suspect that their favorable reception has owed everything to that attitude.) In the early 1960s, there was a controversy going on between two schools of thought in linguistics and the philosophy of science, the Katz and Fodor controversy. I think Fodor was in the minority at that time, at least among the most prestigious professors in the United States. Fodor said that if we wanted to know about language, we should find out how the language is used, by watching a variety of people using it. His opponents said that, if they were competent to speak the language, they didn't need to do anything except to think, to understand everything about the language. Fodor was an empiricist, his opponents were rationalists. In mathematics, most people are still rationalists. A large school of contemporary thought about computers, called "Artificial Intelligence," is operating within a rationalistic framework. Chomsky's "generative grammar" was ultra-rationalistic, and was easy to set up in computers, though it was perfectly useless in itself. Some physicists hold a philosophy of science that is essentially rationalistic. In Plato's time, all knowledge could supposedly be derived by introspection and the analysis of innate ideas, and education consisted in "drawing out" the knowledge that was innate. (Aristotle, who didn't subscribe to Plato's rationalism, has nevertheless been blamed for holding opinions that weren't sufficiently supported by observation. This was probably because he occasionally relied on the opinions of others, rather than because of any serious defect in his philosophical-scientific method.)

It's important to remember that Rationalism, as used here, isn't simply a "love of reason," which is what is often meant when people speak of "rationalism." In its historical use among philosophers, rather

than being just a devotion to rationality, it is a specific doctrine which denies that experience is the source of knowledge. Historically, Rationalism has been closely allied with mysticism, as an affirmation that knowledge comes from a source beyond the ordinary world of experience and beyond the individual. At the present time, it serves authoritarian science rather than authoritarian theology, though the basic doctrine is the same.

Several contemporary schools of literary theory, sociology, anthropology, even biology, trace their ideas back to Ferdinand de Saussure's analysis of language, reading into it a highly rationalistic doctrine for which there is no actual basis. Saussure's most important idea was that it is impossible to analyze language into its structural units without simultaneously seeing its use in relation to the world of meanings. Without its meanings, it just isn't language. This is a profoundly antirationalist insight, since it shows that symbols take their existence from the experience of communication. But once the symbols exist, they function by the ways they establish distinctions, "this" being defined by the ways it has been used in distinction to "those," "that," etc. Every time a word is used, its meaning changes a little, since every use occurs in a new communicative situation. The contemporary rationalistic academic trends prefer to isolate only the principle of "meaning through opposition," since it supports the rationalistic illusion of operating strictly on the symbolic level. The "symbolic level" is only an abstraction, and doesn't exist independently.

A few decades ago, there was a movement called General Semantics that tried to make people more conscious of the way symbols relate to reality. Their ideas were based on a distinction between the "concrete" use of symbols, and the various levels of abstraction. These distinctions, however, made sense only within a certain theory of how language works, which I think was wrong: It asserted that, if time and space were divided into sufficiently small units, symbols and language could be precise and factual. It ignored the distinction between reality as experienced, and reality as represented in theory. If you keep subdividing a person, John Smith, into smaller moments, you find that there is nothing that represents the known person. The person that you are really referring to is actually a summation of many moments—the summation is the only "concreteness." The person you know is a synthesis, and it is that imaginative synthesis of facts to which the

concrete symbol refers. Generality exists in our knowledge of the world, and the distinction between concrete and abstract is likely to create confusion, and reinforces a specific ideological system. Incidentally, the word "concrete" derives from the roots "grown" and "together," so it is very close in its core meaning to "synthesis." A well constructed generalization can be concrete, and a seemingly simple term, such as "electron," can be "abstract." (Blake said that a line, no matter how finely divided, was still a line; a line exists in our imaginative synthesis of the world, and it is only a denial of that synthesis that can divide its unity into "infinitesimals.")

Mathematics has its value in representing certain relationships or patterns, but the rationalistic illusion that the meaning is independently contained and fulfilled by the "algorithm," has led many people into dogmatisms and serious errors. "Coefficients of reality" are often neglected. In practice, you are not very likely to be mistaken if you assume that mathematical descriptions of physical states are always erroneous.

In the 17th and 18th centuries, progress in technology and industry was already making rationalism seem inadequate, but it still served the social purpose of allowing the ruling class to claim that the doctrines it wished to enforce had the support of timeless, innate and universal principles. There was supposed to be a Great Chain of Being, a hierarchy in which the king and the lords were just below the angels, and Reason was a mathematically clear description of the way things were, and should be. As the chain of being finally broke up at the end of the 18th century, the king brought in the Rev. Malthus to explain how war, poverty, and disease served the divine, or kingly, purpose, by controlling population growth, justifying misery and social antagonism in a new way.

There were philosophers, such as John Locke and David Hume, who argued that much of our knowledge is gained through the senses, and there were satirists, such as Henry Fielding, who ridiculed the supposedly divinely sanctioned class system, but Blake took a much simpler, but more radical position, in saying that "Reason isn't the same that it will be when we know more," and that reason is only the ratio of things that are presently known, and not the source of new knowledge. Blake kept the idea that experience is the source of knowledge, without reducing "experience" to the "senses." Blake didn't deny the existence of some innate ideas; he didn't think we were born as a "blank slate," but

there is more to the mind than what we are born with. Imagination and invention and mental striving were able to generate new forms. This commitment to experience as the source of knowledge, rather than just analyzing a stock of "innate ideas," made Blake's world one that was oriented toward the future, toward invention and discovery, rather than to memory, established knowledge, and tradition. In its essence, it was antidogmatic.

Rationalism is a system of symbols, in which each symbol is demonstrated to have its own proper place and status. To the extent that reason is held to be "innate," the system will be prescriptive and judgmental, rather than simply descriptive, explanatory, and illuminating. When an alternative system is proposed, it may be considered a "heresy," if the system from which it dissents is both rationalistic and authoritarian.

Except for the dangers involved in committing a heresy, it is very easy to follow the implications of the system that one finds in one's own mind, since self-assertion contains no principle of corrective contradiction. Essentially, rationalism consists of thinking something is true because you thought of it.

I think of the philosophical Rationalists as being the bureaucrats of the mind, making everything tedious and boring and repetitive. Eliminating Rationalism, then actual individualized full mental life can begin.

Even a heresy, if it is based on rationalism, is past-oriented, and dogmatic. Over the years, scholars have ascribed most of the important heresies, as well as mainstream religious ideas, to Blake. Whatever interpretive system the scholars favor, they are able to find it in Blake's work. Calling Blake "a mystic" is especially useful when the goal is to claim that the critic is getting at the deepest levels of meaning in Blake, even though there is no clear meaning for the word in contemporary English, and Blake didn't use the term in a way that suggested he would approve of having the word applied to himself.

Blake's notes written in the margins of books make it clear that he wasn't simply adopting anyone's doctrinaire opinions, and that he was able to find useful ideas in the thoughts of others even when he disagreed with them on important issues. Blake was not a rationalist, but he agreed with Bishop Berkeley's understanding of the importance of distinguishing thought from language. He recognized that Descartes, Locke, Hume, Newton, had inadequate ideas about the nature of "matter," but he didn't

accept the simplistic doctrine of extreme rationalism that matter doesn't exist.

When people consider Leonardo de Vinci, they usually make the point that he had mastered every field of knowledge, and so the question of "sources" and "influences" doesn't come up. In the 18th century, London was the cultural center of the world; European, Asian, and ancient cultures and ideas were discussed in books, magazines, and conversations. Being an engraver, a painter, a poet, and a political activist, Blake's circle of acquaintances was as wide as anyone's could be. England has had, probably since the 17th century or earlier, a counter-culture of opinionated dissenters. I suspect that the people who spent several years studying the classics for a university education were somewhat culturally deprived, relative to the people who participated in the rich unofficial culture, where new ideas in art, science, and philosophy were being discussed. London was also the center of a world-spanning empire, a tyrannical class-system, and an industrial-commercial revolution. The past and the possible futures could be seen from Blake's vantage point.

Among all the published opinions about things that influenced Blake, I have seen only a few discussions of his treatment of scientific ideas, mainly his rejections of Newton's mathematical and physical assumptions, and very few comments on Blake's position on the major philosophical controversies of his time. A biologist, Jacob Bronowsky, wrote a book about Blake, but Bronowsky's own biological, historical, and linguistic ideas were relatively conventional. Even though Blake's work is full of images from biology, the critics ignore the fact that Emanuel Swedenborg published very advanced biological research in the middle of the 18th century, and that Erasmus Darwin was known for presenting his ideas on biological evolution in poetry (especially Zoonomia). The title of Blake's book, The Four Zoas, has apparently never led scholars to ask whether it had anything in common with Zoonomia. Even though Blake made many disparaging remarks about Swedenborg's religious books, many people have claimed that Blake was influenced by Swedenborg's religious doctrines, while ignoring the possible influence of the scientific work.

Although the idea that "contradiction produces change" is associated with Hegel's "Dialectic," it was an old and well known theme in philosophy. When Blake's idea, that "without Contraries there is no progression," is seen in context, I think it is appropriate to think that

to a great extent, Blake derived the idea from a consideration of the sexes. "Generation," so often discussed in relation to the biblical "fall of man," always leads to the issue of the productive interaction of the sexual contraries. The issue of sexual love permeates Blake's work. I suspect that Blake produced even more explicitly sexual work, but since most of his work wasn't really published, when his wife died in 1831, the bulk of his manuscripts and paintings were subject to the whims of their unsophisticated owners. But on the basis of his existing work, it is reasonable to say that sexual and imaginative energy was the motor that Blake saw producing intellectual advancement. This male-female principle of change was more fully explored by Blake than by anyone previously, since he made it concrete and personal, rather than abstract. Working in history, human energy ran into the constrictive, limiting elements, the tyrannies of policy, philosophy, and commerce. For Blake, the interaction of energy with those limits became a philosophy of freedom and revolution.

While Blake discussed the importance of perception in understanding the world, he was remarkable in the care he took to make it clear that he saw the world "all alive," in which grains of dust or sand, birds, worms, ants, flies, etc., perceived and experienced in ways that were not different from those of human life. Bishop Berkeley, who said that the material world outside the philosopher's mind doesn't exist, added as an afterthought that it exists in the mind of God. If consciousness is the only guarantee of existence, there was no problem in the existence of Blake's world, in which everything was alive and conscious.

Everyone finds it almost obligatory to describe The Lamb as a symbol for Jesus, but then they find the Tyger's symbolic meaning more problematic, and—from Coleridge in the early 19th century down to the newest publications at the end of the 20th century—people are boggled by the "obscurity" of The Fly. But in that poem, Blake makes it clear that there is no obscure symbolism, when he says "then am I a happy fly, if I live or if I die," etc. The animal poems are expressions of Blake's evolutionary, vitalistic, cosmology. The tyger, at least, would be too much for a creationist doctrine to handle. If worms and flies and ants are conscious and in the same situation as human beings, the bonds of sympathy and forgiveness are universal.

In a world that's alive and developing, new knowledge is always possible, and imagination has the prophetic function of reporting the

trends and processes of development, illuminating the paths toward the future. Reason is subordinate to invention and discovery.

The dualistic conception of matter as distinct from energy and consciousness is a constrictive illusion put in place by the forces of empire, and the living reality would be freed from the inert husks of the wrongly conceived natural world, when in the future the world was freed of tyranny. After Blake, it would be nearly another century before others would see that the crude materialism of Newton and the Natural Philosophers was essentially a life-denying culmination of the worst trends of official religious dogma.

A complete survey of Blake's references to Christianity would be voluminous, and not all of them are immediately clear, and require a careful placing in the context of the ideas that were being discussed in London at that time. But it's hard to reconcile the common description of him as a mystic with his reference to "Old Nobodaddy aloft," or with his comment that Jehovah gives us a knock on the head, and Jesus soothes it. He always defines god in human terms, so from the conventional viewpoint, he would probably be considered as an atheist or pantheist, but he didn't describe himself or his friends as atheists. When people called Tom Paine an atheist, Blake defended him against the charge. Other friends, Mary Wollstonecraft and William Godwin, were sometimes called atheists, but in their writings, they never expressed very unconventional religious ideas. When we recall that in the early 1990s, George Bush expressed the idea that atheism should be illegal, it is easy to imagine that people in 18th century England wouldn't have felt that it was safe to be called atheists.

In 1803, Blake apparently said something like "damn the king," while getting a drunk soldier out of his yard, and was tried for sedition or treason. He was acquitted, because his far more scurrilous written comments hadn't been published, and it didn't occur to the government to look for documentary evidence to support their case. The fact that he printed his own work, and sold only a few copies of his books to affluent friends, probably saved his life, but it accounts for his obscurity during his own lifetime.

Tom Paine's writing was published and widely read in prerevolutionary America, but he was considered a criminal in England, and Blake was credited with saving his life by helping him escape to France. Politically and ethically, Blake's writing is similar to that of Paine, Godwin, and

Wollstonecraft (often called the "first feminist"), but his language is usually more vivid. It was probably the clarity of his political opposition that made his work unpublishable during his lifetime. The first "complete" collection of his work was published in 1927, and until that year, very few people had seen more than a few of his most famous poems.

Blake printed his work by hand, without a press, by writing the text backwards on copper plates, surrounded by his drawings, and then etching away the surrounding copper, so that the image remained elevated, and could be inked and printed as if it were a wood-block. If he hadn't devised this method for printing a few copies of his books, it isn't likely that much of the work would have survived.

Shortly after the French Revolution, William Wordsworth was associated with the Blake-Wollstonecraft-Godwin group's defense of the revolution, but he moved away from the ideals of that group, and adopted more socially acceptable ideas. He finally became England's poet laureate. Liberty, equality, and brotherhood were replaced by blandly conformist ideas.

The type of individualism that Wordsworth came to advocate was interesting because it was a rejection of exactly that part of Blake's belief that Blake considered to be the essence of Christianity, namely, forgiveness, brotherhood, and bonds of sympathy connecting all beings. In its place, Wordsworth adopted a memory-centered doctrine. During Wordsworth's lifetime, his ideology was exceedingly successful, but its rationalistic overtones have kept it tied to the past; it had nothing to offer the future. I think we can get some insight into Wordsworth's mind by considering that, on the basis of reading Blake's Songs of Innocence and Experience, he decided that they were written by an insane person. (Blake was aware that slow-witted people, who couldn't follow unconventional thoughts, often considered him to be crazy.)

Everywhere in Blake's work, it is clear that he never underestimated the possibilities of the future, and never imposed false limits onto anything, but he didn't tolerate vagueness or empty abstraction. Sharp definition was essential, and unique particulars were the basis for beauty and knowledge.

For Blake, the dialectical principal was a feature of the world itself, but it also informed his method, his technique, and his "rhetoric." One of Blake's powerful insights was that intellectual clarity is achieved by contradiction, opposition, contrast, making distinctions as well as

comparisons. The principle of intensification through opposition had special features when it was developed in his painting and writing. Blake gave much of the credit for his style of thinking to the process of spending thousands of hours in the practice of etching. The image you create in the conventional etching technique is made when acid "bites" into the lines that will be inked; in Blake's new technique, the image is made permanent by the acid's corroding away of everything except the sharply defined image. The decisive, dividing, line is essential. Anyone who has spent even a few hours of intense effort working in dry-point or etching understands that, when you stop, the appearance of the world is altered by changes that have taken place in your eyes and brain. Often, his "metaphors" are literal imaginative insights that have great generality. This kind of knowledge distinguishes the work of a craftsman from that of an academic. The probability is that Blake's art led him to appreciate compatible ideas when he found them, and it doesn't seem likely that he was "influenced" by them the way an academic is influenced by books, since Blake had his own "sources" that are generally neglected by intellectuals.

Blake found that contrasts made meanings clear, and made language vivid. Heaven and Hell, Clod and Pebble, Lamb and Tyger, Angel and Devil, Greek and Jew, Innocence and Experience, presented contrasts that encouraged the reader to think about the range of possibilities Blake had in mind. He was always consciously trying to energize the reader's mind to get out of dogmatic ruts, to look at things freshly, so he often used the polarities in ways that would surprise the reader, ironically reversing familiar references. A pious commonplace would be contrasted with the disturbing realities that it normally hid. Both in his writing and in conversation, Blake was often playful and teasing, and over-serious people have usually taken him too literally.

Academic commentators are so often attached to their erudite pieties that it seems that they can't read English. In the 18th century, a clod meant just what it means in the 20th century, either a lump of dirt, or a lunkhead. In the Clod and the Pebble, when the Clod speaks the properly sanctimonious phrases, justifying its oppressed misery with a dogma, we have a clue regarding Blake's attitude, but then he makes it perfectly clear by speaking of Heaven's despite, literally, Heaven's malice (a concept that appears many times in different forms in other parts of his work). Either the commentators assume that the word "despite" had

a different meaning in the 18th century (it didn't), or they assume that Blake made an error of diction, because they choose to alter the meaning to "despite Heaven." Just as judges aren't allowed to change the wording of the laws that they interpret, literary experts aren't allowed to rewrite texts to make them better suit their interpretation.

The same insensitivity to the world of concrete experience that has allowed so many commentators to read their own ideas into Blake, ignoring what he said in plain English, makes satire and irony and sarcasm inaccessible to many people who otherwise seem intelligent; this is especially apparent when scientists comment on literature. Forming an imaginative synthesis of the writer and his meaning requires mental flexibility and energy, rather than just analytical acuity.

Everyone who described Blake's physical appearance remarked on his large head. Blake commented that he didn't like to travel or undergo physical strain, because of its effects on his health. The brain is an energetically expensive organ, which consumes large amounts of glucose. A very large brain puts a special burden on the liver's ability to store energy, and is likely to make a person conscious of physiological processes. Blake's descriptions of the process of seeing show that he was integrating his experience into his knowledge, describing brain physiology, incorporating his perceptions and the best scientific knowledge that was available to him, into a philosophical description of the place of conscious life in the world. The pulsation of an artery was the unit of time, a red blood corpuscle was the unit of space, enclosing eternity and infinity, eliminating arbitrary and abstract entities, and placing human life within cosmic life, while revealing cosmic life within the individual.

The idea of a "biological cosmos" seems strange only when it is considered against an ideology which maintains that life is alone in an immense dead universe. The assumption of a dead, unintelligent, randomly moving physical world is the creation of a series of theological ideas, which Blake perceived as essentially Satanic. Blake used the language of these theologies, but inverted them, showing the ways they were used to obscure reality, and to impose a perverse way of life onto the living world.

Fred Hoyle, the astronomer, said "If this were an entirely scientific matter, there is little doubt from the evidence that the case for a fundamentally biological universe would be regarded as substantially proven." (1989)

Over the last few decades, biologists feel that they have established the "biochemical unity of life," in which biochemical cycles and genetic codes are widely shared. The idea of ecological interdependence has come to be recognized as an essential part of life, or (as demonstrated by Vernadsky, and suggested by Hoyle) a cosmic principle. Blake often called himself a Christian, and defined Christianity in many novel ways, as art, love, politics, science, but specifically, in his version of Christianity, forgiveness was an essential idea, and nothing lives for itself only. Blake's Christianity as Art was a concrete part of living, and he ridiculed some of the abstract theosophical definitions of god that were common in his time. When his remarks are considered against the background of Spinozistic pantheism, it is the intensification and personalization, the avoidance of abstractions that could permit the attribution of passivity or inertness to any part of reality, that stand out. When he said that the world is alive, he meant that it is a defect of perception that makes Newton's world seem passive, empty, and dead. A few years ago, a movement that called itself "deep ecology" tried to absolutize the ideas of ecology; Blake's view of the interactive unity of life was as well thought out as any that preceded Vernadsky's cosmology.

Rather than elevating any of the ideas of Christianity to an absolute doctrine, Blake used them as parts of an organic whole. The principle of forgiveness was presented as the appropriate response to a world which is always new. The desire for vengeance comes from a delusive commitment to the world of memory. Virginity is constantly renewed in the world of imaginative life. While Blake said that you can't forgive someone until they stop hurting you, the desire to be forgiven indicates that there is an opportunity to resolve the problem.

Although most mathematicians and computer-so-called-scientists are committed to a rationalistic, past-oriented view of their mental operations, and some scientists accept that ideology along with mathematics, the valid, discovery-oriented sciences have to be future-oriented. A first step in avoiding dogmatic assumptions might be phrased as "remembering what you are," a living being, and asking how you know things: The interaction with other beings, exchanging energy and information with the environment, experiencing yourself in the world.

Holistic medicine and holistic psychology came into existence as attempts to overcome the dogmatic compartmentalization of reality that is endemic. Whenever rigidity is a problem, looking for ways to create new

patterns that by-pass the petrified pattern can lead to a solution. Parkinson's disease and other physical problems have been approached using techniques of intensified or varied stimulation. Increased stimulation—even electromagnetic stimulation—appears to open alternative patterns. Music, dance, and swimming have been used successfully to improve fluidity in various neurological diseases. Kurt Goldstein (The Organism) worked with brain injuries, and found that the brain has a variety of ways to restore a new balance. Raising the amount of energy that's available can allow natural processes to create a better synthesis. Political and social problems that are culturally determined may follow rules similar to those of organic brain disease.

Optimal assumptions, when assumptions are necessary, are those that don't commit you to undesirable conclusions. For example, in the 1950s, some people made the assumption that nuclear war was inevitable, and made large investments in "fallout shelters," which were conceived in terms of world war II bomb shelters, and so resources were diverted from other investments, such as education, which didn't in themselves foreclose future possibilities. Self-fulfilling prophecies and self-limiting assumptions are often built into supposedly practical activities.

The assumption that cancer is genetically determined, and the assumption that regeneration is impossible in the heart or brain, are self-limiting assumptions that have been immensely destructive in biology and medicine. There was no reason to make those assumptions, except for the rationalist culture. Physics, biology, and cosmology are manacled by many unnecessary assumptions. The limits of adaptation, the extent of life's potential, can't be discovered unless you look for them, but the sciences have built many artificial limitations into their systems.

Avoiding unnecessarily limiting assumptions, looking for patterns rather than randomness, looking for larger patterns rather than minimal forms, avoiding reliance on verbal and symbolic formulations, expecting the future to be different—these are abstract ways of formulating the idea that the world should be seen with sympathetic involvement, rather than with analytical coldness.

Almost everything which has been denounced as "teleological" has turned out to be much closer to the truth than the mechanistic views that were promoted as "more scientific," and many horrors have been committed by people who have said that nature shouldn't be "anthropomorphized," that subjective feelings shouldn't be attributed to "the

experimental material." The surgeons who operate on babies without anesthesia are operating on the assumption that any being which can't say "I'm going to sue you" is unable to experience pain.

When we analyze the ideas of chemical reaction equilibrium (burning something, for example), or biological adaptation or growth or learning, and see that they are strictly directional in time (which is the basic meaning of "teleological"), and consistent with Aristotle's description of causality, we can see the mysticism that has been imposed on our culture with the idea that "teleological explanations are unscientific."

Blake was clearly aware that the reason for making limiting assumptions was to maintain control, and to profit from another's suffering. Seeing that the sadistic assumptions that were put in place to regulate human life rested on a dichotomizing of soul from body, Blake's correction was to replace them with a unity of consciousness and substance, a living world rather than a dead world.

An imaginative study of his work has the potential to rouse one's abilities and to open an unlimited world of possibilities. "I give you the end of a golden string, Only wind it into a ball, It will lead you in at Heaven's gate, Built in Jerusalem's wall." Blake knew that his work, like anything new in the world, could be understood only by an active mental process.

Every communicative act is original, and understanding it is an invention, a projection, an imaginative synthesis. We can sometimes finish another person's sentence, the way we anticipate the notes in a melody; we predict the intended meaning. If the symbols carried the meaning in a passive rationalistic way, the person receiving the symbols would receive nothing new. Intellect is a process of imaginative synthesis, or it is nothing.

Blake devised "a system" that would make it possible to think about the world without unconsciously making a commitment to the false limits. He showed, by working within this new philosophical synthesis, that Art, Science, and Politics are structurally and substantially interdependent. The question I asked in the title, "can art instruct science?" isn't the right question once you see the world from Blake's perspective, since Science is Art, and both must be based on experience and imagination.

Blake used, in a new way, the things that were available in his culture, to reveal the process of creation, on all its levels. He consciously used language in a new way, to free the reader from the stereotypes of con-

ventional language. His methods are relevant, as he knew they would be, for other times and situations.

Notes and Quotations

I happened to read Swedenborg's scientific work just as I was getting interested in concentrating on becoming a biologist, and I realized that it was his scientific knowledge that shows up in Blake's imagery, far more than his theology, which Blake obviously despised. By chance, just after I finished my master's thesis on Blake, I got a job at a Swedenborgian college (Urbana University), where I saw in traditional form the small minded theologism that Blake had seen in Swedenborg. As a result of those experiences, I greatly appreciated the book, The Heaven and Hell of William Blake, by Gholam-Reza Sabri-Tabrizi, which apparently hasn't been very well received academically.

Blake's imagery indicates that he had a great interest in the physical and biological sciences, and he apparently had some direct contacts with the leading scientists in London, some of whom are lampooned in Island in the Moon. Some of Swedenborg's discoveries were probably discussed in these groups.

Although Swedenborg's original works in anatomy and physiology were probably his most impressive contributions, he was also a pioneer in paleontology, cosmology (the nebular hypothesis, in particular), magnetism, crystallography, metallurgy, and endocrinology.

E. P. Thompson's Witness against the Beast is an extremely valuable source for clarifying Blake's vocabulary.

Synectics, W. J. J. Gordon, Harper & Row, 1961. Describes how metaphorical thinking was used for solving practical problems, in the Synectics Research Group in Cambridge, Mass.

In the "scientific" philosophies of Blake's time, it was common to speak of matter and its primary and secondary qualities. Blake understood that this view of matter was a derivative of awful theologies:

> And this is the manner of the Sons of Albion in their strength
> They take the Two Contraries which are calld Qualities, with
> which
> Every Substance is clothed, they name them Good & Evil
> From them they make an Abstract, which is a Negation

Not only of the Substance from which it is derived
A murderer of its own Body: but also a murderer
Of every Divine Member: it is the Reasoning Power
An Abstract objecting power, that Negatives every thing
This is the Spectre of Man: the Holy Reasoning Power
And in its Holiness is closed the Abomination of Desolation

What is a Church and What Is a Theatre? are they Two & not One? Can they Exist Separate?
Are not Religion & Politics the Same Thing? Brotherhood is Religion
O Demonstrations of Reason Dividing Families in Cruelty & Pride!

And he who takes vengeance alone is the criminal of Providence;
If I should dare to lay my finger on a grain of sand
In way of vengeance; I punish the already punishd: O whom
Should I pity if I pity not the sinner who is gone astray!

"Imagination has nothing to do with memory." (comment on Wordsworth).

"Knowledge is not by deduction, but Immediate by Perception or Sense at once." (comment on Berkely).

With Demonstrative Science piercing Apollyon with his own bow!

Generalizing Art & Science till Art & Science is lost.

"For Art & Science cannot exist but in minutely organized Particulars"

Since the difference between a Rationalistic view of the world and a creative view is largely a question of the reality of time, it's worth mentioning the work of an astronomer whose cosmological view was based on the reality of time: N. A. Kozyrev.[1] J. Narlikar more recently did similar work, including his collaboration with H. Arp, described in Arp's *Seeing Red: Redshifts, Cosmology, and Academic Science*, Apeiron, Montreal, 1998.

Cancer

Disorder and Energy

Ray Peat's Newsletter, 2014

ACCORDING to the World Health Organization, cancer is now the leading cause of death in the world. Although many "causes" are known, and despite the "War on Cancer," nothing practical has been done to reduce the incidence of cancer.

Since Nixon started that war, the number of people dying annually in the U.S. has increased faster than the population. In ancient Rome and Egypt, cancer was rare; cancer has been identified in only one Egyptian mummy. In the U.S. and several other countries, between 2002 and 2005 there was an unprecedented decline (7% in the U.S.) in the incidence of breast cancer, when the medical use of estrogen decreased following the Women's Health Initiative report showing that estrogen caused cancer, dementia, strokes and heart attacks. However, when the public was reassured about estrogen's safety, breast cancer incidence began increasing again each year.

The cancer industry has been flexible and imaginative in ways of presenting "age standardized" death rates to show that they are making progress against cancer, but there are philosophical and scientific problems in "oncology" (i.e., the study or treatment of lumps) that should be considered by anyone who plans to do business with that profession.

In the 19th century (in Johannes Muller's lab), cancers, like other animal tissues, were found to be made up of cells, and by 1858, all diseases were said to be caused by disturbances in cells (Rudolph Virchow). The atomic and molecular theory of matter was becoming accepted at the time that animals were found to be made up of cells, and in both cases the "elementary particles" seemed to have a special power to explain things. This idea of a cellular basis of disease gradually displaced the old idea that diseases were caused by an imbalance of the body fluids, or humors. In 1863, Virchow recognized that inflammation, involving leukocytes, was a common feature of cancer, but that aspect of his work was neglected for a long time.

Recent medical textbooks reveal no major change in the understanding of cancer since Virchow's time, except that "genes" (which weren't known during Virchow's life) gradually became the most important

aspect of cells. The typical modern textbook describes the cellular disturbance of cancer as the result of an "initiating" mutation in a gene, which gives it the potential to develop into a cancer, if it subsequently is exposed to a "promoter," which causes it to multiply. In some versions of the theory, a promoter is a second mutation that causes proliferation, but in other versions the promotion is caused by chemicals binding to receptors the way hormones do, to stimulate proliferation. Typically, textbooks (and reports of continuing research) describe subsequent changes in the genes that cause a cancer to progress from a simple excess of cells through stages of increasing malignancy: hyperplasia, dysplasia, carcinoma in situ, invasive cancer.

One of the reasons that the medical understanding of cancer hasn't changed significantly since Virchow's time is that blaming misbehaving cells for causing a tumor fits into the older medical tradition, that has existed at least since the time of Hippocrates, 400 BC, which treated tumors either by cutting them out, or by burning them off with caustics. Virchow's identification of misbehaving cells provided a clear mental image of exactly what the physician must try to destroy. And it's probably hard to get interested in something which could seriously limit your professional activities if it turned out to be true.

The "cellular basis of cancer" was developed simultaneously with the germ theory of disease, and in the case of cancer, the deviant cells came to be considered an alien substance, "not-self," analogous to infective germs. Paul Ehrlich's search for poisons that were specific for bacterial pathogens was quickly extended to the idea of finding poisons that would distinguish between cancer cells and the patient's cells. Hippocrates' therapeutic approach to cancer may have survived for 2400 years, but the ideas of his younger contemporary, Plato, about order and causation have probably had a greater effect on medicine. Plato believed that the world of experience is inferior and accidental, and that there are timeless "Forms" that are the real substances. In the atomic theory of matter, eternal, unchanging atoms took the place of platonic forms, and there are still molecular biologists who insist that life can only be explained in terms of its constituent atoms ("What else is there but atoms?"). This philosophy of timeless forms was a deep commitment of people like Gregor Mendel and August Weismann, whose ideas dominated the thinking of early 20th century geneticists. Genes were the immutable essence of organisms, and the cells, tissues, and organs that form the

organism are merely temporal and accidental. Weismann's "germ plasm" or germ line contained the immortal genes, the rest of the body lacked them, and was essentially mortal.

For most of the 20th century, the official doctrine was that most of the cells of the adult body became stationary once the body reached its adult size, and that aging consisted of the "wearing out" of those mortal cells. When a tumor, containing new cells, would appear and grow, these cells were called "immortal," because they didn't follow the rule for normal, stationary, mortal cells. Their "immortality" is often demonstrated by growing them endlessly in culture dishes. Normal cells, if they can be made to survive in a culture dish, are likely to be "transformed" into cancer, demonstrated by their ability to replicate in dishes.

This is an important ideological point, that developed as biologists were experiencing the extreme difficulty of getting cells to replicate, or even to survive, in culture dishes. It has only recently been realized that cells need more than nutritional and hormonal signals to survive in culture; they require certain textural, structural, even rhythmically repeating conditions that mimic their surroundings in the living body. Applied to cancer, the gene theory made it seem clear that the changes occurring in tumor cells were irrevocable, and it has seemed self-evident to oncologists that the only hope the cancer patient has is for the physician to destroy every bit of the alien substance. The recurrence of a cancer that has been removed has been evidence to them that fragments had remained, or that the cancer had distributed its seeds into other parts of the body. This seems to be the necessary conclusion if cancer is "caused" by defective genes.

New ideas of causality have grown up in science beside, or within, the science culture that is committed to platonism, reductionism, and genetic determinism. A few biologists, including Ana Soto and Carlos Sonnenschein, are applying more realistic ideas of causality to ecological, developmental, and cancer research. They have said "The ecological developmental biology (eco-devo) movement rejects the notion that development is merely the unfolding of a genetic program."[1] If events such as cancer aren't "caused by genes," understanding the causes of cancer and the appropriate ways to treat it will require more holistic ways of looking at the tumor's relation to the organism, and the organism's relation to the environment. It has been more than 40 years since

experimenters demonstrated that cancer cells could be caused to revert to normal, by changing their environment. Harry Rubin[2] has observed that cells can accumulate hundreds of mutations, and still function normally in the organism, but when separated and grown in a culture dish their differences become obvious. The surrounding cells in the body are causing the defective cells to remain normal in appearance, function, and growth behavior, instead of acting like cancer cells, and can also cause "stem-like" cells to differentiate appropriately. He says "Intimate contact between the interacting cells is required to induce these changes." When stem cells enter a tumor, they don't find that regulatory, normalizing interaction with normal cells.

Work like Rubin's shows that even "myriad" mutations don't necessarily cause cancer, and another line of research shows that things which don't cause mutations can cause cancer—the "non-mutagenic carcinogens." The presence of mutations is neither sufficient nor necessary for causing cancer, but tumors do eventually accumulate serious damage, which causes most of the tumor cells to die quickly. Biological stress, or excitotoxic energy deprivation, destabilizes the genome; genetic changes develop as a result of prolonged destructive influences. The "non-genotoxic" carcinogens first cause inflammation, excitation, and energy impairment, leading to fibrosis, and atrophy. Cycles of cell injury, death, and repair cause chromosomes to deteriorate as the tissue loses its organization.

When a cell is stimulated, it responds, and the response requires energy. The stronger and more continuous the stimulus, the more energy the cell needs to continue responding. In some conditions, cells can desensitize themselves, to survive in the presence of continuous stimulation or irritation, but otherwise they are killed when they don't have enough energy to keep responding. When a nerve is stimulated and responds, a wave of negative electrical charge passes through it; the electrical field accompanies a structural change in the cytoplasm of the nerve; similar changes occur in other types of cell. Stimulation of a nerve with negative (cathodal) polarity causes swelling, stimulation with the opposite polarity causes the opposite behavior; when nerve cells are inhibited, they shrink.[3–5]

Swelling, an increase of the water content of an area of tissue, is a general feature of inflammation,[6] whether it's in a lump caused by a bee sting, a bruise, or hives, or a cancer. Besides the instantaneous

uptake of water described by Tasaki, there are increases that continue because of metabolic and chemical changes in the irritated cell. Tasaki has used gels of synthetic polymers to demonstrate that an electrical field can cause these changes, without the need for the "chemical osmotic" changes that are customarily assumed to account for the swelling changes caused by stress.[7] When the pH of a protein gel becomes more alkaline, it swells. The electrical activation of a nerve causes a quick shift towards internal alkalinity,[8] followed by a sudden increase in lactic acid production. Although increased lactic acid causes acidity of an irritated or inflamed region, the conversion of pyruvic acid to lactic acid causes the interior of the stressed cell to become more alkaline, causing it to swell. This is the same process that causes the familiar swelling of tired muscles.

If blood vessels swell, the delivery of oxygen may be restricted, and hypoxia causes more intense swelling, because more lactic acid is produced, and less oxidized. This swelling pressure resembles an increase of osmolarity. For over 100 years, it has been customary to treat shock with "isotonic" fluids, which are in balance with well oxygenated tissues, with approximately 290 mOsmol/L, but this usually causes edema, swelling, and weight gain. Stressed tissues have been found to be in balance with fluids of much higher osmolarity, for example 372 mOsmol/L,[9] and sometimes much higher.

Apart from its acidity, lactic acid acts as an excitatory signal. A very slight increase above the normal amount of lactic acid in the body fluids excites sensitive cells, and the amounts reached in inflamed tissues and in cancers will excite even stable cells such as myelinated nerves.[10]

Cancer cells show all the signs of being intensely stimulated, and this includes a high rate of oxygen consumption.[11] The stimulation increases the energy requirements beyond the ability of the mitochondria's capacity to meet them, leading to the production of lactate even when a normal amount of oxygen is present. Even when both glucose and oxygen are supplied (which they usually aren't), the tumor cells will consume amino acids as fuel, as well as using them as material for growth. Tumors have been called "nitrogen traps" or "glutamine traps," but this has meaning beyond the use of the nitrogen for growth; it is involved in the energetic inefficiency of this process, and the reorganizing effects this wasteful flow of energy has on the tissue structure.[12] When glutamine enters the Krebs cycle to be used as fuel, this interferes with the ability to

oxidize glucose, causing more lactic acid to be formed, contributing to the excitation and increased energy requirement. Lactic acid activates the other major mediators of inflammation, including prostaglandins (made from PUFA), free fatty acids (including arachidonate, that forms prostaglandins[13]), nitric oxide, carbon monoxide, proteolytic enzymes that degrade the extracellular matrix, TNF,[14] hypoxia inducible factor,[15,16] interferon, and interleukins. Arachidonic acid itself can increase lactate production.[17] TNFalpha and interferon gamma activate lactic acid production by increasing prostaglandins.[18]

Most of the present information about cancer cells' behavior, such as reactions to radiation and chemical toxins, has been based on the study of cells in culture dishes. For more than 70 years, it was generally believed that radiation caused mutations and cancer by directly modifying the cells' genetic material. Then, it was discovered that fresh cells that were added to a dish of irradiated cells also developed mutations. The radiation causes cells to emit excitatory, inflammatory, substances such as serotonin and nitric oxide, which injure the cells that are later put near them.

Applying this information to the existing knowledge that radiation induces cancer in animals, the doctrine of genetic determinism inferred that the radiation "bystander effect" is just another mechanism by which radiation produces the "mutant cancer cell" or clone of cancer cells. But the difference between events *in vitro* and *in vivo* is that cells which are injured in the organism immediately initiate a process of healing, and in that situation each of the substances emitted by injured cells is acting both locally and systemically to activate repair or regeneration of the damaged tissue. Cells isolated in a culture dish can't call on the organism for the necessary materials, so the responses of the "bystander" cells, leading to mutations and death, seem meaningless. The injured cells are merely toxic, rather than potentially being a stimulus to healing. When any part of a living organism is injured, for example by x-rays or surgery, the emitted substances affect the endocrine and nervous systems, activating processes that change metabolism and behavior. The injured tissue takes on new functions, for example by locally synthesizing estrogen, cortisol,[19] and other hormones, as well as stimulating the normal endocrine glands to secrete them. These interactions have been generally disregarded in cancer treatment, because of the gene centered theory of cancer, but they are essential for understanding the

"malignancy" of tumors, that property that makes them likely to return after the tumor has been destroyed, and to spread to other tissues. Has anyone ever heard of a radiologist or surgeon who measured estrogen or the various mediators of inflammation before, during, and after their treatments? Long range survival after breast cancer surgery is affected by the time in the menstrual cycle when the surgery is done.[20]

All sorts of stress, inflammation, and tissue injury increase the concentration of estrogen, both locally and systemically. Estrogen in turn produces hypoxia, swelling, lactic acid formation, and stimulates cell multiplication. Even a brief period of hypoxia will cause the secretion of lactate and other chemoattractants,[21] which will cause cells to move into the hypoxic area from the blood stream. Although lactic acid attracts immune cells, it probably reduces their anticancer functions, and it stimulates the formation of new blood vessels, supporting continued growth and expansion of the multiplying cells.[22] When a tissue is being repaired normally, the new cells sense a quorum, and stop multiplying. The return of nerves to the damaged area is part of the regenerative process; nerves have inductive and stabilizing effects on differentiating cells.

These complex interactions between tumor cells and the rest of the organism are not considered by the ideology of medical oncologists. The ruling belief is that the malignancy of cells can be determined by examining them microscopically, and that their rate of growth can be determined, and that the tumor's approximate time of origin can be estimated. After surgically removing a tumor, the administration of chemotherapy and/or radiation is governed by mathematical descriptions of the expected behavior of cancer cells.

The mathematical relation of mortality to aging was described by Benjamin Gompertz, an actuary, in 1825, based on the understanding that people become less able to resist dying as they get older. This Gompertzian growth curve, which is realistic when applied to a population of people, flies, or rabbits, was applied to tumor growth.[23] Gompertz' reasoning that the probability of a person's dying increases with age has nothing to do with cancer cells, and there is very little evidence that his law of growth is useful for describing tumors. Laird's evidence consisted of 19 tumor samples, taken from 10 mice, 8 rats, and a rabbit. Her suggestion that the continuing deceleration of the growth rate might represent a natural growth regulating process wasn't influential, but her

use of an actuarial formula, suggesting certain properties of cancer cells, has been extremely influential. It seems to be the profession's great need for justification that has made a Law of Tumor Growth so important to them.

At the time Laird did the tumor growth study, there was considerable interest in the idea that the immune system could be induced to prevent tumor growth. In 1951, Chester Southam, of the Sloan-Kettering Institute, tested his theory of cancer immunity on hundreds of patients and prisoners, and his results were widely reported. He found that pieces of tumor implanted in healthy people caused a local intense inflammation, which healed completely after two or three weeks. In sick people, the rejection of the cancer implant took about twice as long, and in people who already had cancer, the implant was very slow to be destroyed, and sometimes it was still present when they died. In 1889, Stephen Paget had noticed that cancers metastasize only into certain organs, and compared the cancer cells to seeds that "can only live and grow if they fall on congenial soil." While many people, like Southam, saw a failing "immune system" as part of the congenial soil, and suggested vaccination to activate an immune rejection of the tumor, others have suggested "reducing the soil to dust," making growth impossible in a more general way. Recently, this attitude has taken the form of different ways of "starving" cancer, by reducing sugar in the diet, or by blocking cells' ability to use sugar. The idea of making the "soil" inhospitable to cancer is a variation on the theme of killing the unwanted tissue.

As long as the lump is defined as an alien material, killing it by any means seems reasonable, but if it is seen as the body's attempt to repair itself, then killing it is no more reasonable than it would be to cut the spots out of someone with smallpox. When a cell is dying, it emits growth stimulating signals.[24] That's a normal part of tissue renewal. Some of its substance guides the differentiation of new cells, as demonstrated long ago by Polezhaev (discussed in my previous article, *Stem Cells, Cell Culture, and Culture: Issues in Regeneration*). Anything that injures a tissue enough to require cells to be replaced causes the activation of a regulatory protein, hypoxia-inducible factor, HIF, which inhibits mitochondrial respiration, causing a shift toward glycolytic metabolism, increasing substances needed for growth. HIF is essential to the healing of any wound. Even glucose deprivation can cause the induction of HIF. Prostaglandins, made from polyunsaturated fatty acids

released by stimulation, can cause HIF to increase, but HIF also causes prostaglandins to increase. Lactic acid increases the expression of HIF, while HIF causes cells to shift metabolically to depend on converting glucose to lactic acid, that is, to adopt the "cancer metabolism." HIF is recognized as a fundamental problem in "cancer therapy," since HIF allows the cancer to resist the treatment, but the treatment increases HIF.

Radiation, chemotherapy, and surgery all activate these processes of cell replacement, and unless something has changed to improve the organism's recuperative ability, it isn't clear why the cells which replace the missing part should be more able to satisfactorily complete the recovery process than the original cells were. Even the amount of radiation in a single dental x-ray is enough to activate the excitatory-inflammatory processes, and a "therapeutic" x-ray to any part of the body excites similar, but much greater, processes throughout the body. But the ideology of "the cancer cell," and the Gompertz Growth Law, guide the practice of cancer treatment.

Many years ago, Harry Rubin was impressed by hearing from a pathologist that he had been able to find diagnosable cancer somewhere in the body of every person over the age of 50 that he had autopsied. If everyone has cancer by the age of 50, that means that cancer is harmless for most people, and that small cancers might frequently appear, and be spontaneously removed as part of the body's regular house-cleaning. One of the reasons that spontaneous regression of tumors seems so rare is undoubtedly that most tumors are quickly cut out by surgeons.

Preventing injury should be a basic consideration, but the medical slogan, "first do no harm," just doesn't apply to the cancer treatment industry, and this results from the doctrine of "the cancer cell," which is something to be destroyed or kept from multiplying. In the process of diagnosing a cancer, and during the course of treating it, the patient is usually subjected to multiple x-ray examinations, sometimes given radioactive drugs that supposedly concentrate in hidden tumors to emit positrons, and often has toxic contrast agents injected even for MRI examinations. These procedures, even before the destructive "therapies" begin, are adding to the body's inflammatory burden, interfering with the body's ability to complete a healing process. Decisions about pain control usually disregard the effects of the drugs on tumor growth and

general vitality—for example, the opiates stimulate histamine release, which increases inflammation and tumor growth.

In 1927, Bernstein and Elias found that rats eating a fat free diet had almost no spontaneous cancer, and many studies since then in animals and people have shown a close association between polyunsaturated fatty acids and cancer. The polyunsaturated fatty acids in themselves, and their breakdown products, are excitatory and destabilizing to normal cells, but by modifying the sensitivity and energy production of cells, they limit cells' ability to respond to stimulation and destabilizing influences. Although they aren't essential for wound healing,[25] they and their metabolites, the prostaglandins, are very conspicuous in wounds and tumors, and their proportion generally increases with aging. The prostaglandins are involved in several vicious cycles, including that with HIF mentioned above. This makes the PUFA and prostaglandins important to consider in relation to optimizing wound healing, and decreasing cancerization. Aspirin's protective and therapeutic effects in cancer are starting to be recognized, but there are several other things that can synergize with aspirin to reduce the circulation of free fatty acids and their conversion to prostaglandins. Niacinamide, progesterone, sugar, carbon dioxide, and red light protect against both free fatty acids and prostaglandins.

Since excitation leads to intracellular alkalinity and swelling, reducing the excitation seems reasonable, and many things which protect cells against excitation also have demonstrated anticancer effects. Local anesthetics, antihistamines, and antiinflammatory substances and some anesthetics such as xenon[26] are safe. Inhibitory substances related to GABA are being investigated for their ability to stop tumor growth. Simply stopping excessive excitation tends to restore the dominance of oxidative respiration over glycolysis.

To restore the supply of oxygen, sugar, and nutrients, swelling must be stopped. Hyperosmotic fluids act directly on swollen cells, removing water. Stopping excitation allows a return to efficient metabolism and reduces the injury potential, allowing the pH to decrease; with lower pH, the cell releases some of its water.

Increasing carbon dioxide lowers the intracellular pH, as well as inhibiting lactic acid formation, and restoring the oxidation of glucose increases CO_2. Inhibiting carbonic anhydrase, to allow more CO_2 to stay in the cell, contributes to intracellular acidification, and by system-

ically increasing carbon dioxide this inhibition has a broad range of protective anti-excitatory effects. The drug industry is now looking for chemicals that will specifically inhibit the carbonic anhydrase enzymes that are active in tumors. Existing carbonic anhydrase inhibitors, such as acetazolamide, will inhibit those enzymes, without harming other tissues. Aspirin has some effect as an inhibitor of carbonic anhydrase.[27] Since histamine, serotonin,[28] and estrogen[29,30] are carbonic anhydrase activators, their antagonists would help to acidify the hypoxic cells. Testosterone[31] and progesterone are estrogen antagonists that inhibit carbonic anhydrase.

With aging, cells have less ability to produce energy, and are often more easily stimulated. The accumulation of polyunsaturated fats is one of the factors that reduce the ability of mitochondria to produce energy.[32,33] Increased estrogen exposure, decreased thyroid hormone, an increased ratio of iron to copper, and lack of light, are other factors that impair the cytochrome oxidase enzyme.

The increased intracellular alkalinity and intracellular calcium that result from the combination of those factors increase the tendency of cells to be overstimulated, leading to aerobic glycolysis, the cancer metabolism. Improving any part of the system tends to increase carbon dioxide and decrease lactate, permitting differentiated functioning.

There are many people currently recommending fish oil (or other highly unsaturated oils) for preventing or treating cancer, and it has become almost as common to recommend a sugar free diet, "because sugar feeds cancer." This is often, incorrectly, said to be the meaning of Warburg's demonstration that cancer cells have a respiratory defect that causes them to produce lactic acid from glucose even in the presence of oxygen. Cancer cells use glucose and the amino acid glutamine primarily for synthetic purposes, and use fats as their energy source; the growth stimulating effect of the "essential fatty acids"[34,35] shows that depriving a tumor of those fats retards its growth. The great energetic inefficiency of the cancer metabolism, which causes it to produce a large amount of heat and to cause systemic stress, failure of immunity, and weight loss, is because it synthesizes fat from glucose and amino acids, and then oxidizes the fat as if it were diabetic.

Estrogen, which is responsible for the fact that women burn fatty acids more easily than men, is centrally involved in this metabolic inefficiency. When a tissue is exposed to estrogen, within minutes it takes

up water, and begins to synthesize fat, with a tendency to produce lactic acid at the same time. The alkalizing effect of lactic acid production is apparently what accounts for the uptake of water. Since it takes longer, at least 30 min, to produce a significant amount of new enzymes, these early changes are explained by the activation of existing enzymes by estrogen.

The transhydrogenases, or the transhydrogenase function of the steroid dehydrogenases, which shift metabolic energy between glycolytic and oxidative systems, have been shown to explain these effects of estrogen, but the transhydrogenases can be activated by many stressors. The biological function of the transhydrogenases seems to be to allow cells to continue growth and repair processes in a hypoxic environment. Estrogen can start the process by creating new pathways for electrons, and will promote processes that are started by something else, and progesterone is estrogen's natural antagonist, terminating the process.

Recently, a group at Johns Hopkins University[36] has been working out the implications of this ability to change the metabolism under hypoxia: Using an isotope-labeled amino acid, "…glutamine import and metabolism through the TCA cycle persisted under hypoxia, and glutamine contributed significantly to citrate carbons. Under glucose deprivation, glutamine-derived fumarate, malate, and citrate were significantly increased." The implication of this is that if the tumor isn't supplied with sugar, it will increase the rate at which it consumes the host's proteins. Forty years ago the work of Shapot and Blinov was showing the same effect, except that they demonstrated the involvement of the whole organism, especially the liver, in interaction with the tumor.[37]

The alkaline cancer cell surrounds itself by the acid that it emits, and this extracellular acidity increases the ability of fatty acids to enter the cell;[38] cancer cells, although they are synthesizing fat, also avidly take it up from their environment.[39] This fat avidity is so extreme that cancer cells *in vitro* will eat enough polyunsaturated fat to kill themselves. This has been offered as proof that fish oil kills cancer. Saturated fats, however, have a calming effect on cancer cells, inhibiting their aerobic glycolysis[40] while permitting them to resume the respiratory production of energy.

The foods that nourish the patient well enough to support healing while permitting energy reserves to be built up are also the foods that don't interfere with the hormones, that don't cause spurious excitation

of the tissues. The polyunsaturated fats directly stimulate the stress hormones, activate the excitatory amino acid signals, and directly excite cells, while the saturated fats have opposite effects, and are anti-inflammatory, and also don't interfere with mitochondrial function. When we eat more carbohydrate than can be oxidized, some of it will be turned into saturated fats and omega-9 fats, and these will support mitochondrial energy production. Carbohydrates in the diet also help to decrease the mobilization of fatty acids from storage; niacinamide and aspirin support that effect. Sugars are probably more favorable than starches for the immune system,[41] and failure of the immune system is a common feature of cancer. Polyunsaturated fats are generally known to suppress the immune system. Foods that provide generous amounts of sodium, calcium, magnesium, and potassium, help to minimize stress. Trace minerals and vitamins are important, but can be harmful if used excessively—iron excess is important to avoid.

Emodin, an anti-inflammatory substance found in cascara sagrada bark and other plants, is similar to other molecules that have been used for treating cancer, and one of its effects is to lower HIF: "Consistently, emodin attenuated the expression of cyclooxygenase 2 (COX-2), VEGF, hypoxia inducible factor 1 alpha (HIF-1α), MMP-1 and MMP-13 at mRNA level in IL-1 and LPS-treated synoviocytes under hypoxia".[42] MMP-1 and MMP-13 are collagenase enzymes involved in metastasis. When cells are fully nourished, supplied with protective hormones, and properly illuminated, their ability to communicate should be able to govern their movements, preventing—and possibly reversing—metastatic migration.

Cascara, Energy, Cancer and the FDA's Laxative Abuse

Ray Peat's Newsletter, 2012

THE medical culture and the general culture share some attitudes about the nature of the most common ailments—colds, cancer, arthritis, constipation, heart problems, etc., and they often agree about which things can be treated at home, and which require special medical care.

These background ideas are important because they influence the actions of insurance companies, legislators, and regulatory agencies. They also influence the judgments people make about their own health, and, too often, the way physicians treat their patients.

The prevalence of chronic constipation in North America has been estimated to be 27 %, and in a ten year study, the occurrence of new cases was about 16 %—the prevalence increases with aging. In some studies, women are 3 times as likely as men to suffer from constipation. A recent Canadian article commented that "While chronic constipation (CC) has a high prevalence in primary care, there are no existing treatment recommendations to guide health care professionals."

Almost everyone in the U.S. is familiar with the idea of "laxative abuse," of using laxatives when they aren't absolutely necessary, and with the idea that chronic laxative use will create a dependency, the way an addictive drug does. Contemporary doctors are likely to prescribe stool softeners for constipated old people, rather than "stimulant laxatives," probably because "softener" doesn't have the pejorative connotation that "stimulant drug" has—not because there is a scientific basis for the choice.

Many doctors advise constipated patients to drink more water and exercise. While there is some physiological basis for recommending exercise, the advice to drink more water is simply unphysiological. A study in Latin America found no evidence of benefit from either of those recommendations, and recommended the use of fiber in the diet. The right kind of fiber can benefit a variety of bowel problems. However, some types of fiber can exacerbate the problem, and some types (such as oat bran) have been found to increase bowel cancer in animal studies.

Despite the greater prevalence of constipation in women and older people, even specialists in gastroenterology are very unlikely to consider the role of hypothyroidism or other endocrine problems in chronic constipation.

Because of the cultural clichés about constipation—that it's caused by not eating enough fiber or drinking enough water, for example—and the belief that it's not very important, there is seldom an effort made to understand the actual condition of the intestine, and the causes of the problem.

Aging and stress increase some of the inflammatory mediators, tending to reduce the barrier function of the bowel, letting larger amounts of bacterial toxins enter the bloodstream, interfering with energy metabolism, creating inflammatory vicious circles of increasing leakiness and inflammation.

Often people visualize something like a sausage casing when they think of the intestine, but when the intestine is becoming inflamed its wall may swell to become an inch thick. As it thickens, the channel narrows to a few millimeters in diameter, and may even close in some regions. In the swollen, edematous, inflamed condition the contractile mechanism of the smooth muscle is impaired. The failure of contraction is caused by the same structural changes that increase permeability.[1–7]

Obviously, in the very swollen, structurally deformed intestine, with almost no lumen, neither a stimulant nor a simple fibrous bulk could restore functioning, because even with stimulation the smooth muscle is unable to contract, and the closed channel won't admit bulk. Even gas is sometimes unable to pass through the inflamed intestine. Mechanical thinking about the intestine fails when inflammation is involved; now that inflammation is known to play an important role in Alzheimer's disease and heart disease, it will be more acceptable to consider its role in constipation.

The contractile ability of smooth muscle, that's impaired by swelling and inflammation, can be restored by antiinflammatory agents, for example aspirin (or other inhibitor of prostaglandin synthesis) or antihistamines. This applies to the muscles of lymphatic vessels,[7–9] that must function to reduce edema, as well as to the bowel muscles that cause peristalsis.

If someone thinks of constipation as the result of a lack of neuromuscular stimulation, then it might seem reasonable to design a drug that

intensifies the contractions produced by one of the natural transmitter substances, such as serotonin, histamine, or acetylcholine. That's apparently what Novartis did, with tegaserod, a drug that increases the bowel's sensitivity to serotonin. That drug, called Zelnorm, was approved by the FDA in 2002, after a couple of years of publications praising it. At the time of its approval, there was already evidence that people using it were more likely to have abdominal surgery, especially for gallbladder disease, and there was doubt about its effectiveness.

Strangely, the drug was approved to be used for only 4 to 6 weeks, taking two tablets daily without interruption. When patients benefitted from the first treatment, they might be eligible for an additional 4 to 6 weeks, but then it would be necessary for them to find another way to deal with their constipation.

Zelnorm side effects: abdominal pain, chest pain, flushing, facial edema, hypertension, hypotension, angina pectoris, syncope, arrythmia, anxiety, vertigo, ovarian cyst, miscarriage, menorrhagia, cholecystitis, appendicitis, bilirubinemia, gastroenteritis, increased creatine phosphokinase. back pain, cramps, breast cancer, attempted suicide, impaired concentration, increased appetite, sleep disorder, depression, anxiety, asthma, increased sweating, renal pain, polyuria. (Later, it was found to cause heart attacks and intestinal ischemia/necrosis.) Why would the FDA approve a drug, without evidence that it was more effective than harmless things that were already widely available?

Zelnorm Prices: In the U.S., Novartis estimates that Zelnorm tablets will sell for somewhere in the range of $3 to $4 each. The drug is expected to generate $1 billion in annual sales for Novartis.

During the years just before the new drug was approved, there were several publications reporting that emodin, the main active factor in cascara, a traditional laxative, had some remarkable antiviral and anticancer activities. Other studies were reporting that it protected against some known mutagens and carcinogens. Less than 3 months before approving Zelnorm, the FDA announced its Final rule[10] "Certain Additional Over-the-Counter Drug Category II and III Active Ingredients." "the stimulant laxative ingredients aloe (including aloe extract and aloe flower extract) and cascara sagrada (including casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, and cascara sagrada fluidextract)," determining that they "are not generally recognized as safe and effective or are misbranded. This final rule is

part of FDA's ongoing OTC drug product review. This rule is effective November 5, 2002."

Historically, the FDA has ruled against traditional generic drug products when the drug industry is ready to market a synthetic substitute product.

In 2007, the FDA withdrew its approval for Zelnorm, but allowed it to be licensed as an "Investigational New Drug." "On April 2, 2008, after more than eight months of availability, the company has re-assessed the program and has made a decision to close it. Novartis is in the process of communicating this decision to physicians participating in the program. Patients who had access to Zelnorm via this program are instructed to discuss alternative treatment options with their physicians."

Cascara and aloe are not among the treatment options approved by the FDA, so cascara isn't widely available (though anyone can grow aloe plants easily). However, there is considerable interest in the drug industry in the possibility of developing products based on emodin, or aloe-emodin, as anticancer or antiviral drugs. Even if it were proved to be safe and effective for use as a laxative, its potential use as an alternative to extremely profitable cancer and virus treatments would make it a serious threat to the drug industry.

Although the standard medical journals have only recently begun writing about it as a cancer treatment, emodin and related chemicals have been of interest as a non-toxic way to treat cancer, allergies, and viral and bacterial diseases for a long time.

In 1900, Moses Gomberg demonstrated the synthesis of a stable free radical (triphenylmethyl), but for years many chemists believed free radicals couldn't exist. A student of Gomberg's, William F. Koch, came to believe that cellular respiration involved free radicals, and experimented with the metabolic effects of many organic molecules, quinones of several kinds, that can form free radicals, looking for the most useful ones.

For more than 50 years the U.S. Government and the main medical instititutions actively fought the idea that a free radical or quinone could serve as a biological catalyst to correct a wide variety of health problems.

A free radical has an unpaired electron. In 1944 Yevgeniy Zavoisky devised a way to measure the behavior of unpaired electrons in crystals, but it was many years before it was recognized that they are essential to

cellular respiration. Alex Comfort demonstrated them in living tissue in 1959.

By the time coenzyme Q_{10}, ubiquinone, was officially discovered, Koch had moved to Brazil to continue his work with the biological effects of the quinones, including the anthraquinone compound of brazilwood, which is used as a dye. He also used a naphthoquine, lapachon Although vitamin K was identified as a quinone (naphthoquinone) not long after CoQ_{10} was found to be a ubiquitous component of the mitochondrial respiratory system, it wasn't immediately recognized as another participant in that system, interacting with CoQ_{10}.

Although Koch was unable to publish in any English language medical journal after 1914, his work was widely known. In the 1930s, Albert Szent-Györgyi, following Koch's ideas about electrons in cells, interacting with free radicals, began working on the links between electronic energy and cellular movement. Since free (or relatively free) electrons absorb light, Szent-Györgyi worked with many colorful substances. When he came to the U.S. in 1947, and wanted to expand his research, a team of professors from Harvard investigated, and told the government funding agency that his work didn't deserve support. For the rest of his life, he worked on related ideas, expanding ideas that Koch had first developed.

Emodin and the anthraquinones (and naphthoquinones, such as lapachone) weren't the reagents that Koch considered the most powerful, but emodin can produce to some degree all of the effects that he believed could be achieved by correcting the cellular respiratory apparatus: Anti-inflammatory, antifibrotic,[11] antiviral, antidepressant, heart protective, antioxidant, memory enhancing, anticancer, anxiolytic and possibly antipsychotic.

Working backward from these effects, we get a better perspective on the "laxative" function of emodin and cascara. Koch and Szent-Györgyi believed that cellular movement and secretion were electronically regulated. In one of his demonstrations, Szent-Györgyi showed that muscles could be caused to contract when they were exposed to two substances which, when combined, partially exchange an electron, causing an intense color reaction, but without causing an ordinary chemical (oxidation-reduction) reaction. This kind of reaction is called a Donor-Acceptor reaction, and it is closely related to the phenomenon of semiconduction. The reacting molecules have to be exactly "tuned" to each other, allowing an electron to resonate between the molecules.

In a muscle, any D-A matched pair of molecules would cause a contraction, but the same molecules, combined in pairs that weren't exactly tuned to each other, failed to cause contraction. Szent-Györgyi believed that biological signal substances operated in a similar way, by adjusting the electronic balance of cellular proteins.

An effective laxative (besides preventing inflammation) causes not only coordinated contraction of the smooth muscles of the intestine, but also adjusts secretions and absorption, so that an appropriate amount of fluid stays in the intestine, and the cells of the intestine don't become water-logged.

In the presence of bacterial endotoxin, respiratory energy production fails in the cells lining the intestine. Nitric oxide is probably the main mediator of this effect.

The shift from respiration to glycolysis, from producing carbon dioxide to producing lactic acid, involves a global change in cell functions, away from specialized differentiated functioning, toward defensive and inflammatory processes.

This global change involves a change in the physical properties of the cytoplasm, causing a tendency to swell, and to admit dissolved substances that normally wouldn't enter the cells.

The interface between the cells lining the intestine and the bacteria-rich environment involves processes similar to those in cells at other interfacial situations throughout the body—kidney, bladder, secretory membranes of glands, capillary cells, etc. The failure of the intestinal barrier is especially dangerous, because of the generalized toxic consequences, but the principles of maintaining and restoring it are general, and they have to do with the nature of life.

Some leakage from the lumen of the intestine or the lumen of a blood vessel can occur between cells, but it is often claimed that the "paracellular" route accounts for all leakage. (Anthraquinones may inhibit paracellular leakage.[12]) When a cell is inflamed or overstimulated or fatigued, its cytoplasmic contents leak out. In that state, its barrier function is weakened, and external material can leak in. This was demonstrated long ago by Nasonov, but the "membrane" doctrine is incompatible with the facts, so the paracellular route is claimed to explain leakage. Since the cells that form the barrier begin to form regulatory substances such as nitric oxide when they are exposed to endotoxin, it is clear that major metabolic and energetic changes coincide

in the cell with the observed leakiness. Permeability varies with the nature of the substance, its oil and water solubility, and the direction of its movement, arguing clearly that it isn't a matter of mere holes between cells.

Besides endotoxin, estrogen, vibrational injury, radiation, aging, cold, and hypoosmolarity, increase NO synthesis and release, and increase cellular permeabilities throughout the body.

Estrogen excess (relative to progesterone and androgens), as in pregnancy, stress, and aging, reduces intestinal motility, probably by increasing nitric oxide production. The anthraquinones inhibit the formation of nitric oxide, which is constantly being promoted by endotoxin.

Cells regulate their water content holistically, and, to a great extent, autonomously, by adjusting their structural proteins and their metabolism, but in the process they communicate with surrounding cells and with the organism as a whole, and consequently they will receive various materials needed to improve their stability, by adjusting their energy production, sensitivity, and structural composition.

When these intrinsic corrective processes are inadequate, as in hypothyroidism, with increased estrogen and serotonin, extrinsic factors, including special foods and drugs, can reinforce the adaptive mechanisms. These "adaptogens" can sometimes restore the system to perfect functioning, other times they can merely prevent further injury. Sometimes the adaptogens are exactly like those the body normally has, but that are needed in larger amounts during stress. Coenzyme Q_{10}, vitamin K, short-chain fatty acids, ketoacids, niacinamide, and glycine are examples of this sort—they are always present, but increased amounts can improve resistance to stress.

Another kind of adaptogen resembles the body's intrinsic defensive substances, but isn't produced in significant quantities in our bodies. This type includes caffeine and the anthraquinones (such as emodin) and aspirin and other protective substances from plants. These overlap in functions with some of our intrinsic regulatory substances, and can also complement each other's effects.

Emodin inhibits the formation of nitric oxide, increases mitochondrial respiration, inhibits angiogenesis and invasiveness, inhibits fatty acid synthase,[13] inhibits HER-2 neu and tyrosine phosphorylases,[14,15] and promotes cellular differentiation in cancer cells.[14] The anthraquinones, like other antiinflammatory substances, reduce leakage

from blood vessels, but they also reduce the absorption of water from the intestine. Reduced water absorption can be seen in a slight shrinkage of cells in certain circumstances, and is probably related to their promotion of cellular differentiation.

All of these are basic antistress mechanisms, suggesting that emodin and the antiinflammatory anthraquinones are providing something central to the life process itself.

Zelnorm was said to "act like serotonin." Serotonin slows metabolism, reduces oxygen consumption, and increases free radicals such as superoxide and nitric oxide; the production of reactive oxygen species is probably an essential part of its normal function. Emodin has an opposing effect, increasing the metabolic rate. It increases mitochondrial oxygen consumption and ATP synthesis, while decreasing oxidative damage.[16–18]

The Zelnorm episode was just an isolated case of a drug company's exploiting cultural beliefs, with the FDA providing a defensive framework, but the contrast between tegaserod and emodin hints at a deeper and more deadly problem.

W.F. Koch's approach to immunity emphasized the role of energy in maintaining the coherence of the organism, in which toxins were oxidized and made nontoxic. There was no emphasis on destruction either of bacteria or of cancer cells, but only of the toxic factors that interfered with respiration. He demonstrated that the udders of healthy cows could contain more bacteria than those with mastitis, but the bacterial toxins were absent after the cows were treated with his catalyst. He identified the "activated carbonyl group" as the essential feature of antibiotics, the same group that makes coenzyme Q_{10} function in the respiratory system.

Koch's understanding of the oxidative apparatus of life, as a matter of electron balances, involved the idea that molecules with a low ionization potential, making them good electron donors, amines specifically, interfered with respiration, while quinones, with a high affinity for electrons, making them electron acceptors, activated respiration. The toxic effects of tryptophan derivatives, indoles, and other amines related to the behavior of their electrons. (Serotonin wasn't known at the time Koch was doing his basic research.) Koch believed that similar electronic functions were responsible for the effects of viruses.

Both chemical and physical interactions of substances cause electrons to shift in each substance, according to its composition. The shift of electrons accounts for the ability of adsorbed molecules or ions to form multiple layers on a surface, and changes in the electrons of a complex biological molecule affect the shape and function not only of that molecule, but of the molecules associated with it. Interactions of the large molecules of cells, and their adsorbed substances, tend toward stable arrangements, or phases. The type of energy production, and the nature of the regulatory molecules that are present, influence the stability of the various states of an organism's cells.

Koch and Szent-Györgyi were applying to biology and medicine concepts that were simultaneously being developed in metallurgy, electrochemistry, colloid and surface science, and electronics. They were in the scientific mainstream, and it was the medical-pharmaceutical industry that moved away from this kind of exploration of the interactions of substances, electrons, and organisms.

For Koch, antibiotics and anticancer agents weren't necessarily distinct from each other, and would be expected to have other beneficial effects as well.

But an entirely different view of the immune system was taking over the medical culture just as Koch began his research. Mechnikov's morphogenic view, in which the essential function of "the immune system" was to maintain the integrity of the organism, was submerged by Ehrlich's approach, which emphasized killing pathogens, and at the same time, the genetic theory of cancer was replacing the developmental-environmental theory.

Following the early work on the carcinogenicity of estrogens, and the estrogenicity of carcinogens such as polycyclic aromatic hydrocarbons from soot, a few German and French chemists (e.g., Schmidt and the Pullmans) began calculating the high electron densities of highly reactive regions of the anthracene molecule, showing formally why certain molecules are carcinogenic.

At that time, their work was compatible with a developmental view of cancer. But the fact that the polycyclic molecules could interact with the new model of the DNA gene caused the Pullmans' work to be reduced to nothing but a minor theory of mutagenesis.

Anthraquinones, because of the presence of several oxygen molecules, had low electron densities and were stable. The tetracy-

clines, with related structure, have some similar properties, and are antiinflammatory, as well as antibiotic.

When a polycyclic bacterial antibiotic, adriamycyn (later called doxorubicin), was found to be too toxic to use as an antibiotic, the fact that it was toxic to cancer cells caused it to be developed as a cancer drug. It continued to be widely used even after it was found to cause heart failure in many of the "cured" patients, because of its "success" in killing cancer cells.

The fact that many kinds of cancer cells can be killed by emodin makes it slightly interesting as a cancer drug, but its simple generic nature has caused the drug industry to look for a more Ehrlichian magic bullet; for example, they are still looking for ways to keep doxorubicin from destroying the heart.

Emodin isn't a magic bullet (in fact it isn't a bullet/toxin of any sort), but when combined with all the other adaptogens, it does have a place in cancer therapy, as well as in treating many other ailments.

None of the basic metaphors of mainstream medicine—receptors, lock-and-key, membrane pores and pumps—can account for the laxative, anticancer, cell-protective effects of emodin. The new interest in it provides an opportunity to continue to investigate the effects of adjusting the electrical state of the cell substance, building on the foundations created by William F. Koch, Albert Szent-Györgyi, and Gilbert Ling.

Cataracts

Water, Energy, Light, and Aging

Ray Peat's Newsletter, 2014

THE lens replacement surgery is now sometimes recommended when a cataract has caused only a slight decrease in visual acuity, or even a suspected decrease in acuity. I haven't known anyone who had the surgery who had been informed of the incidence of complications of the surgery, which result in permanent blindness for thousands of the patients every year.

Some of the causes of cataracts have been known for many years, but the knowledge is usually ignored by the medical profession. Medical myths about the causes of disease support present practices. Myths about the causes of cancer, heart failure, hypertension, menopause, osteoporosis, sarcopenia, depression, dementia, and cataracts are designed to reinforce each other, forming an interlocking system, an ideology of the organism.

The conventional ideology identifies pathological cells and defective proteins and bad genes as the causes of organ failure and disease, and "aging" is seen as a dimension in which entropy tends to increase those defects.

This ideology discourages thoughts of "field" effects in which the function of a molecule, a cell, or an organ affects, and is affected by, things that aren't in direct contact with it. This is why the removal of a lens is treated so casually. There is some knowledge about the effects of systemic disease on the eye, but very little about the effects of particular parts of the eye on systemic physiology, and relatively few physicians are aware of the effects of one part of the eye on the other parts of the eye. A few of these physiological interactions within the eye are very interesting. For example, injury to the lens powerfully stimulates regeneration of nerves in the retina.[1] Things which injure the lens enough to cause cataracts to develop might also be injuring the retina, but the emission of stimulating substances from the lens must be a compensating influence.

Every normal tissue of the eye is emitting substances that affect other parts of the eye, and probably other parts of the body. Until the 1970s, the literature was dominated by the view that the lens was a

lifeless material, like hair and toenails, and even in 2013 there is great reluctance of researchers to recognize its vital cellular activity.

After an artificial lens has been implanted, there are great changes in the vitreous humor (which fills the space between the retina and the lens), with a reversal of the gradient of viscosity, and with changes in many proteins, including transthyretin, alpha antitrypsin, retinoic acid binding protein, antioxidant proteins, and the enzymes carbonic anhydrase and triosephosphate isomererase.[2]

I haven't seen any recent studies of the effects of lens removal on the nervous system, but a 1953 study of 21 patients reported a high percentage of behavioral disturbances following the surgery: "Following the operation 20 patients showed some alteration in behavior including changes in mood, psychomotor disturbances, paranoid and somatic delusions, hallucinations, disorientation and confabulations. In 3 cases the disturbance was characterized as severe." "It is concluded that disturbed behavior is an integral part of the reaction of almost all cataract patients because of a complex interaction of a number of factors".[3]

In animal studies, when the lens capsule is closed after removal of the lens, within a few weeks a well formed lens has regenerated;[4] cell division is stimulated in the cells remaining attached to the capsule, similar to the regeneration of the adrenal cortex after its removal.

Artificial replacement lenses are designed (with an ultrasharp edge) to block the regenerative migration of cells within the capsule, because the cells can quickly form a new cataract behind the plastic lens; those cataracts commonly form in reaction to the lens. The use of arsenic to kill these cells has been proposed, and probably used.[5]

The easy money in lens surgery has obviously discouraged professional interest in preventing cataracts, or curing them, or stimulating the regeneration of new lenses. Research in the prevention of cataracts has encountered serious barriers to performing the clinical trials that would be necessary for approval. "…Clinicians have even developed the opinion that lens and cataract research is no longer necessary to overcome cataract blindness."[6] However, it isn't inconceivable that someone could find a way to make prevention, cure, or regeneration significantly remunerative.

Although the lens has no blood supply, fluid carrying nutrients and oxygen is constantly flowing through it, providing the cells with glucose, amino acids, and ATP, that it uses for maintaining its structure. Its

proteins are being renewed continually, broken down and synthesized.[7] There is clear evidence that some of the core cells retain a nucleus, and that large molecules can move between cells.[8–11] Despite this evidence, prominent researchers are still promoting the paradigm of inertness, the lens as analogous to a toenail. As in other cells, ATP maintains the proper water content in the cells. Besides providing energy and amino acids, the circulating fluid carries minerals and many hormones and regulatory substances.

The absence of a blood supply to the lens has kept people from thinking of its pathology in terms of the inflammatory processes that are now recognized in other conditions, for example in dementia, heart disease, and cancer, but the same basic processes can be seen in the development of cataracts. Improved knowledge of lens physiology is very likely to lead to major improvements in therapies for the other conditions. In the lens, the state of water changes before there is any other evidence that a cataract is developing;[12] detecting similar water changes in other tissues might improve diagnosis and treatment of other problems. Things that acutely lower the ATP content of cells increase their water content, and in the process, the water functions differently, becoming more randomly arranged.

The idea that the properties of water change as cell functions change contradicts the common reductionist assumption that water is just the medium in which molecular interactions occur. Since Kelvin's 1858 demonstration that the heat capacity of water changes with its shape, and Drost-Hansen's demonstrations that its density decreases near surfaces, attention to the physical properties of water has made it possible to understand many biological mysteries, such as the decrease of volume[13] when a nerve or muscle cell is excited. Although the invention of the MRI grew directly from Damadian's understanding of water's centrality to biology's most important issues, the technology's most important contributions, related to changes in water structure, haven't been recognized, understood, or assimilated by medicine.

The electrical properties of the protein framework of a cell interact with the state of the water in the cell, and with the things dissolved in the water, including phosphate, calcium, sodium, and potassium. Actin, one of the major muscle proteins, forms a meshwork in the cytoplasm of lens fiber cells, and myosin, the other major muscle protein, has been found in association with the actin.[14] ATP (alternating with ADP+inorganic

phosphate) is involved in muscle contraction and relaxation, and it is involved in the conversion of actin from a filament into a globular form. Changes in the amount of ATP and ADP are important for influencing the interactions of water and proteins.

The actin skeleton is involved in the fiber cell's elongation as it develops from a roundish epithelial cell, and it's probably responsible for the ability of lens cells to contract when stimulated.[15,16] These muscle-like effects of actin are believed to be responsible for the movement of organelles and other cell motion, such as cytoplasmic streaming. But, as a major part of the cell's structure, it could also be expected to act as the framework for electroosmotic flow of water, accounting for the circulation that maintains the cell's energy. The observed static electrical properties of lens cell fragments could account for a complete daily renewal of the fluid,[17] but the metabolic gradients in whole cells would probably cause faster flow.

With oxidative energy production occurring in the surface cells, an electrical gradient will be created, causing water to flow away from the site of respiration. (Electroosmosis probably also accounts for the somewhat mysterious exit of water from the eyeball and brain, in perivascular flow.) The flow of water through these cells is very fast, but Ichiji Tasaki has demonstrated similarly fast movement of water in nerves and artificial polymers in association with electrical activity.[18–21]

At least since Gullstrand's unfounded assertions in his 1911 Nobel lecture, it has been assumed that the lens, like a water-filled balloon, keeps the same volume when it flattens, for distant focus.,[22] have shown that "…the lens volume decreases as the lens flattens during unaccommodation." "The lens volume always decreases as the lens flattens." They determined that "…the changes in lens volume, as reflected by the speed of the equatorial diameter recovery *in vitro* cow and rabbit lenses during simulated accommodation, occurred within a physiologically relevant time frame (200 ms), implying a rapid movement of fluid to and from the lens during accommodation." This is the duration of the action potential of healthy heart muscle, though it's probably not as fast as the very superficial changes that Tasaki saw in nerves. It's the sort of change rate that could be expected in an organ whose change of shape is the result of stimulation. Accommodation, with this immediate hydration, is produced by cholinergic stimulation, and in the healthy

lens this hydration is rapidly reversible, as the stimulating acetylcholine disappears and the lens flattens.

The failing heart muscle, unable to relax fully, becomes harder as its water content increases, and cancer cells, locked into a contracted excited state, become stiffer as their water content increases. Similarly, cataracts have been described as more rigid than normal lens tissue,[23,24] yet their water content is higher.[25] Along with the increased water, the stressed cells take up very large amounts of calcium, and sodium increases while potassium decreases. Inorganic phosphate increases in the stressed cells, some of it entering with the circulating fluid, but some of it produced from the ATP which is decreasing. Serotonin, iron, lipid peroxidation products, nitric oxide, and prostaglandin are also increased. The increased calcium activates proteolytic enzymes that break down protein.

In the failing heart and growing tumors, there is an increase in the quantity and the cross-linking of collagen in the extracellular matrix, contributing to the overall hardness, besides the contracted state of the cells themselves. In the cataract, cross-linking of various proteins, including collagen, also seems to be involved in the problem, along with the altered state of the water.[26,27] The cross-linking enzyme transglutaminase is induced by stressors such as ultraviolet light which produce cataracts.

When the available energy doesn't meet the cell's energy requirements, if the cell isn't quickly killed by the stress it will use some adaptive mechanisms, stopping some repair processes to reduce energy expenditure, possibly stopping specialized functions to reduce energy needs. Fibrotic changes occur as a result of defensive reactions in stressed cells, usually following long periods of fatigue and inflammation. Cortisol generally protects cells by blocking over-stimulation and providing increased material for energy and repair, but it can kill cells (nerve cells and thymus cells) that depend on glucose oxidation, leading to immunodeficiency and excitotoxic brain damage. The glucose-dependent lens fiber cells express the same glucose transporters, $GLUT_1$ and $GLUT_3$, as the brain, and the "nerve specific" $GLUT_3$ is concentrated in the dense nucleus of the lens.[28] Exposure to excessive cortisol or hypoglycemia is able to quickly produce cataracts, showing the basic importance of glucose metabolism for lens health.

Oxidative metabolism in the surface cells is probably largely responsible for the streaming of fluid through the fiber cells, providing some ATP and the nutrients that allow the fiber cells to maintain and repair their structure, but I suspect that local metabolism of glucose by the fiber cells provides most of the energy for keeping the protein-water system in its orderly relaxed state.

The aging lens, like all normal tissues, is drier, has a lower water content, than younger tissues, but when a cataract begins to develop, there is a sharp increase in the water content in that area, something that happens in any excited or fatigued tissue. (In a stimulated nerve or muscle, for example, although in a closed system there would be a slight decrease in volume as its water becomes relatively randomized, there is normally a sudden absorption of water from the extracellular space, where the water has the same random organization.) With the decreasing energy charge of the cell, represented by decreasing ATP and increasing ADP and inorganic phosphate, the long range order of the water decreases, changing the activity of enzymes in a variety of ways, for example by the exchange of a high magnesium content for a high calcium content. While the renewal of proteins decreases because of an energy deficit, the activation of proteolytic enzymes by calcium degrades the cell architecture and the crystallin that makes up about 90 % of the cell's protein, and these damaged proteins become progressively cross-linked, in a process analogous to the cross-linking of collagen in sun-damaged skin, or in cancer or a fibrotic failing heart.

The diffusion of water in these congested cataract areas becomes random, more like ordinary bulk water, and it's likely that this randomization of the water, along with the architectural disorganization of proteins and changing electrical fields, impedes the longitudinal flow of nourishing fluid through the lens. MRI studies show relatively free diffusion of water longitudinally in the lens fiber cells from front to back, but not transversely.[29] Water that's highly ordered by nearby surfaces can still be very mobile parallel to the surface.

The parasympathetic nerve transmitter acetylcholine is formed in the lens, as well as its receptor and the enzyme which destroys it, cholinesterase. Chemicals that inhibit cholinesterase, and drugs that mimic the action of acetylcholine on the receptor, cause cataracts. These drugs[30,31] cause the lens to take up water, sodium, and calcium, and to lose potassium, and by increasing the cells' energy expenditure, they

accelerate the consumption of glucose while blocking other metabolism. Since these are known effects of stimulation by acetylcholine, it's reasonable to assume that acetylcholine is involved in the natural formation of cataracts.

Besides the direct excitatory effects of acetylcholine, the increase of intracellular calcium and decrease of magnesium[32] caused by it promote the synthesis of nitric oxide (which, for example, blocks the function of cytochrome oxidase, reducing the production of ATP), and the interference with glucose metabolism in itself is cataractogenic.[33]

Ultraviolet light powerfully stimulates the formation of nitric oxide,[34] and is one of the known causes of cataracts. Since the cornea is more directly exposed than the lens to the ultraviolet rays of sunlight, the effects of injury can be seen more quickly. Exposure of the cornea to ultraviolet light causes swelling, reduced transparency, and the formation of nitric oxide, which enters the aqueous humor.[35,36] Swelling in itself, regardless of the cause, decreases the transparency of the cornea;[37] anything interfering with its energy metabolism causes swelling.

The blue color of ordinary water is caused by its absorption of red light, possibly by its hydrogen bonds,[38] but there haven't been many studies of the physical effects of red light on water itself. Since water absorbs much more strongly in the infrared wavelengths, there is a tendency to explain the benefits of sunlight by its infrared rays. Red and orange wavelengths penetrate tissue very effectively, because of their weaker absorption by water, allowing them to react with pigments in the cell, such as cytochrome oxidase, which is activated (or re-activated) by red light, increasing the production of ATP. This effect counteracts the toxic effects of ultraviolet light, but there are probably other mechanisms involved in the many beneficial effects of red light.

Recent work by a group at the University of Ulm in Germany[39] has revealed an effect of red light (670 nm) on water that I think helps to explain some of its protective and restorative actions. Shining laser light onto layers of water adsorbed on a solid surface, they were able to show "a breathing-like volume expansion of the topmost sheets of water molecules." They explain this as the result of a stabilization of a more ordered state of the hydrogen bonds of the water. They are applying this to chemotherapy, since the expansion of water in the cell where much of the water is in adsorbed layers similar to their experimental set-up, alternating with its volume contraction as the light is pulsed, causes

water to move in and out of the cell quickly, taking some of the drug with it. They have also proposed that degenerative changes in the connective tissues involve a loss of ordered water, and have experimented with light treatments to restore elasticity and flexibility.

Since the water in cataracts is in a less ordered state than in the transparent lens, the re-ordering effect of red light could be valuable, and if the effects are the same as in their experiments with cancer cells, the increased volume of the re-ordered water would cause a movement of water out of the cataract, as it does in cancer cells in their experiment. And the known restorative effect of red light on oxidative production of ATP would almost certainly be helpful.

Among the popular medical treatments that are likely to contribute to the development of cataract are glucocorticoids, and drugs that increase serotonin,[40,41] and drugs that increase nitric oxide. Free fatty acids are toxic to the lens, which contains the enzymes for synthesizing prostaglandins and related promoters of inflammation; the products of lipid peroxidation are increased in people with cataracts. Endotoxin from the intestine increases the formation of nitric oxide, so it's essential to minimize intestinal inflammation.

High altitude very strongly protects against cataracts.[42] Low oxygen tension itself protects the lens's clarity,[43] possibly by the protective effect of increased carbon dioxide against glycation of protein amino groups. Aspirin's known anticataract effect apparently involves a similar protection of crystallin against glycation, but aspirin has several other protective effects, including prevention of protein cross-linking, and the inhibition of the synthesis of nitric oxide and prostaglandins and other disruptive materials.[44–46] Progesterone's inhibition of nitric oxide production is probably protective for the lens, paralleling its effects in other organs. Inhibitors of nitric oxide, such as aminoguanidine, are protective. Anticholinergics, including atropine, inhibit over-hydration of the lens and prevent cataracts caused by excessive cholinergic stimulation.[47] Caffeine, in animal experiments, prevents cataracts. Uric acid, which inhibits nitric oxide formation, is reduced in people with cataracts. The factors that prevent or promote other degenerative diseases are similarly protective or harmful for the lens.

Cholesterol, Longevity, Intelligence, and Health

Ray Peat's Newsletter, 2007

MEDICAL magazines and television stations like to propagate the idea that cholesterol is bad stuff, and as a result, that cliché is known to almost every American. Recent journal articles have promoted the idea that "the lower the serum cholesterol is, the better" it is for the health of the patient.

The theory that heart disease is "caused by cholesterol" has gone through several stages, and most recently the use of the "statin" drugs has revived it in a radical way. One consistent theme for fifty years has been that people should eat more polyunsaturated fat and less saturated fat, to lower their cholesterol, and to avoid butter, cream, eggs, and "red meat," because they contain both saturated fat and cholesterol. Often, medical attention is focused on the fats in the atheroma, rather than on the whole disease process, including clotting factors, vascular spasms, heart rhythm, viscosity of the blood, deposition of calcium and iron in blood vessels, and the whole process of inflammation, including the reactions to absorbed bowel toxins.

Almost 100 years ago, some experiments in Russia showed that feeding rabbits cholesterol caused them to develop atherosclerosis, but subsequent experiments showed that rabbits are unusual in responding that way to cholesterol, and that even rabbits don't develop atherosclerosis from cholesterol if they are given a supplement of thyroid.[1] By 1936, it was clear that hypercholesterolemia in humans and other animals was caused by hypothyroidism, and that hypothyroidism caused many diseases to develop, including cardiovascular disease and cancer. There was already more reason at that time to think that the increased cholesterol was a protective adaptation than to think that it was maladaptive.

The strange idea that cholesterol causes atherosclerosis was revived in the 1950s when the vegetable oil industry learned that their polyunsaturated oils lowered serum cholesterol. (Many other toxins lower cholesterol, but that is never mentioned.) The industry began advertising their oils as "heart protective," and they enlisted some influential organizations to help in their advertising: The American Dietetic Association, the American Heart Association, the US Dept. of Agriculture and FDA, and the AMA. Besides the early rabbit research, which didn't make

their case against cholesterol and might actually have had implications harmful to their argument (since Anitschkow had used vegetable oil as solvent for his cholesterol feedings), the oil industry helped to create and promote a large amount of fraudulent and unscientific work.

The death rate from heart disease in the United States began increasing early in the twentieth century, and it reached its peak from about 1950 to 1975, and then began declining. During the decades in which the death rate was rising, consumption of animal fat was decreasing, and the use of vegetable oil was increasing. In the southern European countries that have been said to show that eating very little animal fat prevents heart disease, the trends after the second world war have been the opposite—they have been eating more animal fat without an increase in heart disease.

The correspondence between heart disease and consumption of saturated fat and cholesterol is little more than advertising copy. If people were looking for the actual causes of heart disease, they would consider the factors that changed in the U.S. during the time that heart disease mortality was increasing. Both increases in harmful factors, and decreases in protective factors would have to be considered.

The consumption of manufactured foods, pollution of air and water, the use of lead in gasoline, cigarette smoking, increased medicalization and use of drugs, psychosocial and socioeconomic stress, and increased exposure to radiation—medical, military, and industrial—would be obvious things to consider, along with decreased intake of some protective nutrients, such as selenium, magnesium, and vitamins.

But those harmful factors all had their defenders: Who defends socioeconomic stress? All of the social institutions that fail to alleviate it. In 1847, Rudolph Virchow was sent to Poland to study the health situation there, and when he returned, the highly regarded anatomist, physiologist and pathologist announced that the Poles wouldn't have a health problem if the government would stop oppressing them, and institute economic reforms to alleviate their poverty. The reforms weren't made, and Virchow lost his job. Other harmful factors, such as seed oils, degraded foods, and radiation, have specific, very well organized and powerful lobbies to defend them.

Despite the growing knowledge about the dangers of polyunsaturated fats, many medical articles are still advocating the "official" heart

protective diet (e.g., "…diets using nonhydrogenated unsaturated fats as the predominant form of dietary fat"[2]).

Some dogs alertly look at the thing a person is pointing at, other dogs just sniff the pointing finger. The publicists who disregard the complete nutritional and ecological situation, to focus on cholesterol and fat in the diet, are like the finger sniffers.

Recent articles in the medical and lipids journals are praising the 1950 work of J. W. Gofman, and the 1914 rabbit studies of N. N. Anitschkow, as the research that revealed cholesterol to be the cause of heart disease. Anitschkow and his co-workers, however, understood that their experiment hadn't explained human heart disease, and John Gofman, about 50 years after publishing his work on the lipoproteins, has done some large studies that could be crucial in disproving the doctrine that has become almost a national religion.

He has shown that mortality from both heart disease and cancer corresponds very closely to the population's exposure to medical services, and specifically to medical radiation. During the peak years of heart disease mortality, medical x-rays gave very large doses of radiation with each exposure, and the population was also exposed to radioactive fallout from atomic bomb testing (explosions from 1945 to 1963 produced a peak of heavy fallout that persisted through the 'sixties and into the 'seventies).

Around 1971, someone noticed that the commercial cholesterol being used in feeding experiments was oxidized, that is, it wasn't really cholesterol. Comparing carefully prepared, unoxidized cholesterol with the oxidized degraded material, it was found that dietary cholesterol wasn't necessarily atherogenic.[3]

Dietitians often recommend eating poached salmon, rather than "red meat," to lower cholesterol. Experimenters have measured the toxic oxidized cholesterol in different foods prepared in a variety of ways. Steaming salmon produced several times as much oxidized cholesterol as frying it, because of the longer cooking time that allowed the polyunsaturated fatty acids to break down, producing toxins such as acrolein and free radicals that oxidize the cholesterol and other components of the fish. The toxic cholesterol content of the steamed salmon was much higher than that of beef cooked at a high temperature.

When oxidized polyunsaturated oils, such as corn oil or linoleic acid, are added to food, they appear in the blood lipids, where they accelerate the formation of cholesterol deposits in arteries.[4,5]

Stress accelerates the oxidation of the polyunsaturated fatty acids in the body, so people who consume unsaturated vegetable oils and fish will have some oxidized cholesterol in their tissues. The constant turnover of cholesterol in the tissues tends to lower the proportion of the toxic oxidized degradation products of cholesterol, but in hypothyroidism, the use of cholesterol is slowed, allowing the toxic forms to accumulate.

Many antioxidant nutrients act like a thyroid supplement did in the 1934 rabbit experiments, preventing atherosclerosis even when extra toxic cholesterol is given to the animals. People who eat seafood get much more selenium in their diet than people who eat nothing from the sea, and selenium is one of the extremely protective nutrients that prevent atherosclerosis in animal experiments with excess cholesterol.

It is well established that several antioxidant nutrients are protective factors in heart disease. The medical establishment has expended a great amount of money and time in the last 60 years fighting the use of vitamin E or selenium for treating or preventing heart disease, though many physicians now take vitamin E themselves. But people who study free radical chemistry recognize that polyunsaturated fats are highly susceptible to oxidation, and that saturated fats tend to slow their degradation, acting to some extent as antioxidants. Several experiments and observations have shown that cholesterol itself can protect against damaging oxidation of polyunsaturated fats, protecting DNA and other vital components of the cell. A consistent program to prevent the oxidation of cholesterol would have to include all of the vitamins and minerals that are involved in antioxidant defense, avoidance of nutrients that exacerbate the destructive oxidations, and an effort to normalize the hormones and other factors, such as carbon dioxide, that have protective effects against free radical oxidation. A low level of cholesterol might increase susceptibility to the oxidants.

The steroids in general, especially those produced in large amounts, progesterone and DHEA, are important parts of the antioxidant defenses. Cholesterol, either that produced internally by the cell, or taken in from the blood stream, is the precursor for all the steroids in the body. Several of the major steroid hormones are antiinflammatory, and cholesterol itself is antiinflammatory.[6,7] Cholesterol also protects against radiation

damage, and many forms of toxins (saponins, cobra venom, chloroform)[8] many more recent studies show that it protects blood cells against hemolysis—breakdown of red blood cells—caused by heat and other harmful agents.[9,10] Cholesterol, vitamin E, progesterone, and vitamin D are considered to be "structural antioxidants," that prevent oxidation partly by stabilizing molecular structures. One of the basic functions of cholesterol seems to be the stabilization of mitochondria, preventing their destruction by stress. Serious stress lowers ATP, magnesium, and carbon dioxide. When ATP and intracellular magnesium are decreased, cholesterol synthesis increases.

During stress, free fatty acids are released from the tissues, and circulating in the bloodstream they are highly susceptible to oxidation. They contribute to the formation of the age pigment, lipofuscin, which is an oxygen-wasting substance that's found in the atheroma plaques in the damaged blood vessels. Iron and calcium accumulation adds to the tissue damage.

The hemolysis which is promoted by polyunsaturated fats and an imbalance of antioxidants and oxidants, releases iron and heme into the blood stream. The incidence of atherosclerosis is increased when the body iron stores are high,[11] probably because of its role in lipid peroxidation and lipofuscin formation.

Especially when the lining of the blood vessel is too permeable, because of the influence of polyunsaturated fats, prostaglandins, estrogen, etc., the heme and iron will enter the endothelial cells, where the iron will catalyze the formation of free radicals, and the heme will be broken down by the enzyme heme oxygenase, into biliverdin, iron, and carbon monoxide, which can contribute to the oxidative stress of the cells. Carbon monoxide makes the blood vessel lining more permeable, allowing fats and fibrinogen to enter the cells.[12]

Although cholesterol is protective against oxidative and cytolytic damage, the chronic free radical exposure will oxidize it. During the low cholesterol turnover of hypothyroidism, the oxidized variants of cholesterol will accumulate, so cholesterol loses its protective functions.

When the metabolic pathways of the steroid hormones were being worked out, an experimenter perfused an isolated ovary with blood. When the amount of cholesterol in the blood pumped into the ovary was increased, the amount of progesterone in the blood leaving the ovary increased proportionately. In the healthy organism, cholesterol

is constantly being synthesized, and constantly converted into steroid hormones, and, in the liver, into the bile salts that are secreted to emulsify fats in the intestine. Thyroid hormone and vitamin A are used in the process of converting cholesterol into pregnenolone, the immediate precursor of progesterone and DHEA. Anything that interfered with these processes would be disastrous for the organism. The supply of cholesterol, thyroid and vitamin A must always be adequate for the production of steroid hormones and bile salts. When stress suppresses thyroid activity, increased cholesterol probably compensates to some extent by permitting more progesterone to be synthesized.

In very young people, the metabolic rate is very high, and the rapid conversion of cholesterol into pregnenolone, DHEA, and progesterone usually keeps the level of cholesterol in the blood low. In the 1930s, a rise in the concentration of cholesterol was considered to be one of the most reliable ways to diagnose hypothyroidism.[13, p. 533] With aging, the metabolic rate declines, and the increase of cholesterol with aging is probably a spontaneous regulatory process, supporting the synthesis of the protective steroids, especially the neurosteroids in the brain and retina.

Many people refer to the structural importance of cholesterol for "membranes," and often imply that the membranes are just at the surface of the cell (the plasma membrane). But in fact cholesterol is found in the nucleus in the chromosomes, bound to DNA and in the nuclear matrix that governs the activation of genes, and in the mitotic spindle, which regulates separation of the chromosomes during cell division: without sufficient cholesterol, cells divide irregularly, producing aneuploid daughter cells (i.e., they have an abnormal number of chromosomes). Aneuploidy is now coming to be recognized as an essential feature of cancer cells. A significant amount of cholesterol was recently discovered to bind to hemoglobin, suggesting that it will be found in association with many other types of protein, when it occurs to anyone to look for it. Osmotic regulation, which is closely involved in cell division and other functions, appears to require cholesterol synthesis.

Around 1985, a big study in Hungary showed that lowering cholesterol with drugs caused a huge increase in the cancer death rate. Hundreds of publications appeared in the U.S. saying that wasn't possible, because low cholesterol is good, the lower the better. The extreme increase in cancer mortality in the Hungarian study was probably the result

of the drug that was commonly used at that time to lower cholesterol, but the pattern of mortality in that study was approximately the same pattern seen in any group with very low cholesterol. In the last 20 years, there have been many studies showing that lowering cholesterol increases mortality, especially from cancer and suicide, and that people with naturally low cholesterol are more likely to die from cancer, suicide, trauma, and infections than people with normal or higher than average cholesterol.

The increased mortality from accidents and suicide when cholesterol is lowered is reminiscent of the problems seen in progesterone deficiency, and it's very likely that a deficiency of the neurosteroids accounts for it. A deficiency of progesterone and other neurosteroids (the steroids synthesized by the nerves themselves) causes depression of mood and impaired learning ability, among other neurological changes. As was the case with cancer, the pharmaceutical industry continues to deny that their anticholesterol drugs cause suicide, depression, and dementia, but there is a large amount of evidence from human as well as animal studies showing that mood and intelligence are depressed by lowering cholesterol. Simply injecting cholesterol into animals can improve their learning ability. In the Framingham heart study of 1894 people extending over a period of about 20 years, people with cholesterol naturally in the "desirable" range, below 200 mg, scored lower on "verbal fluency, attention/concentration, abstract reasoning, and a composite score measuring multiple cognitive domains" than those with higher cholesterol.[14]

After the age of fifty, low cholesterol is clearly associated with an increased risk of dying from a variety of causes. A study of old women indicated that a cholesterol level of 270 mg/dL was associated with the best longevity.[15] "Mortality was lowest at serum cholesterol 7 mmol/L [=270.6 mg], 5.2 times higher than the minimum at serum cholesterol 4.0 mmol/L, and only 1.8 times higher when cholesterol concentration was 8.8 mmol/L. This relation held true irrespective of age, even when blood pressure, body weight, history of myocardial infarction, creatinine clearance, and plasma proteins were taken into account."

The next step in studies of this sort should be to see how the combination of extra thyroid with adequate cholesterol influences longevity. The rising cholesterol that commonly occurs with aging is probably only partial compensation for declining thyroid function, and by optimizing

all of the protective factors, radical changes in the aging process may be possible.

In the roundworm *C. elegans*, which is now a very popular animal for testing aging theories, because its genes and cells have been thoroughly "mapped," it was recently found that adding a gene that simply allows it to synthesize cholesterol, rather than depending on food for its sterols, increased its life span by as much as 131 %.[16] That would be like increasing the human lifespan to about 175 years. These worms are also more resistant than normal to radiation and heat stress.

The cells of the thymus are extremely sensitive to radiation and other stressors, and their enrichment with cholesterol inhibits lipid peroxidation, DNA degradation, and death in response to radiation.[17]

Many high altitude regions of the world have high levels of background radiation, from minerals as well as cosmic rays, so it has been dogmatically believed that mortality from cancer and heart disease would increase with altitude, but the reverse is true. Because oxygen at lower pressure displaces less carbon dioxide from the blood, the body is able to retain more carbon dioxide at high altitude. Carbon dioxide protects against free radicals, and also helps to deliver oxygen to tissues, to maintain efficient energy production, and to prevent cellular stress. One study found 18 times higher incidence of hypertension in low altitude populations than in high altitude people.[18] For many years, these principles have been applied in treating atherosclerosis and other degenerative diseases, in high altitude health resorts. Even a short period of hypoxic treatment can improve the body's ability to eliminate atherogenic lipid peroxides, possibly by improving the stress-resistant functions of the liver.[19–21]

I think editors of medical journals generally see themselves as the purveyors of enlightenment, i.e., as the pushers of the stylish and prestigious doctrines. (Selectivity of evidence to serve the received doctrine is the commonest form of scientific dishonesty.) But because their mental framework is culturally narrow, they sometimes publish things which later could turn out to be embarrassing (if inconsistency could embarrass such types).

The recent discovery that the size of the LDL particle is a predominant factor in the development of atherosclerosis is one of those things that the editors and medical professors should find embarrassing.

Smaller lipoprotein particles have a greater surface area exposed to the oxidative factors in the serum, and so are more rapidly degraded into toxic substances. People with larger LDL particles are remarkably resistant to heart disease, and the drug companies are looking for a way to turn their lipoproteins into products. But the conditions that govern the size of the LDL particles are physically and chemically reasonable, and are causing confusion among the doctrinaire.

There have been several studies in India showing that consumption of butter and ghee is associated with a low incidence of heart disease; for example, according to one study, people in the north eat 19 times more fat (mostly butter and ghee) than in the south, yet the incidence of heart disease is seven times higher in the south. A study in Sweden found that the fatty acids in milk products are associated with larger LDL particles.[22]

In a 35 day study, when butter (20 % of the calories) was compared to various kinds of margarine (with more trans fatty acids) in a similar quantity, the LDL particles were bigger on the butter diet.[23] But in a study of the habitual diet of 414 people, large LDL particles were

found to be correlated with increased intake of protein, animal fat, and trans fatty acids.[24]

In a study of the effect of dietary cholesterol on the atherogenicity of the blood lipids, 52 people were given either an egg diet (with 640 mg. of extra cholesterol per day) or a placebo diet for 30 days. Those whose LDL increased the most on the high cholesterol diet had the largest LDL particle size.[25] They concluded that "these data indicate that the consumption of a high-cholesterol diet does not negatively influence the atherogenicity of the LDL particle."

A similar study in Mexico found that "Intake of 2 eggs/d results in the maintenance of LDL:HDL and in the generation of a less atherogenic LDL in this population of Mexican children".[26]

The estrogen industry tried to get into the heart disease business several times over the last half century, and they are still trying, but the issue of estrogen's harmful effects on LDL particle size is getting some attention. Estrogen clearly decreases the size of the LDL particles.[27] The LDL particles also get smaller at menopause, and in polycystic ovary syndrome, and in preeclamptic pregnancies, all of which involve a low ratio of progesterone to estrogen. But there are still journals publishing

claims that estrogen will protect against heart disease, by reducing the atherogenic response in increasingly mysterious ways.

Occasionally, people have argued not only that estrogen is the factor that protects women against heart attacks, but that androgens predispose men to heart disease. One of their arguments has been that androgens lower HDL, the "good" form of cholesterol. However, there are many studies that show that testosterone and DHEA[28] are protective against atherosclerosis. The LDL particle size is increased by androgens, and postprandial triglyceridemia is decreased.[29]

The studies in the 1930s that showed the protective effects of thyroid hormone against atherosclerosis and heart disease have sometimes been interpreted to mean that the thyroid is protective because it lowers the cholesterol, but since cholesterol is protective, rather than harmful, something else explains the protective effect. Ever since the time of Virchow, who called atherosclerosis arteritis deformans, the inflammatory nature of the problem has been clear to those who aren't crazed by the anticholesterol cult. We are all subject to a variable degree of inflammatory stimulation from the endotoxin absorbed from the intestine, but a healthy liver normally prevents it from reaching the general circulation, and produces a variety of protective factors. The HDL lipoprotein is one of these, which protects against inflammation by binding bacterial endotoxins that have reached the bloodstream. (Things that increase absorption of endotoxin—exercise, estrogen, ethanol—cause HDL to rise.) Chylomicrons and VLDL also absorb, bind, and help to eliminate endotoxins. All sorts of stress and malnutrition increase the tendency of endotoxin to leak into the bloodstream. Thyroid hormone, by increasing the turnover of cholesterol and its conversion into the protective steroids, is a major factor in keeping the inflammatory processes under control.

In hypothyroidism, the pituitary secretes more TSH to activate the thyroid gland, but TSH itself has a variety of pro-inflammatory actions. The C-reactive protein (CRP), which is recognized as a factor contributing to atherosclerosis, is increased in association with TSH. CRP activates mast cells, which are found in the atheroma plaques, to produce a variety of pro-inflammatory substances, including histamine.

The belief that cells are controlled by a plasma membrane, and that cholesterol's main function is to participate in that membrane, has led to a culture that treats cholesterol physiology with little curiosity. A different perspective on the cell starts with a recognition of the lipophilic

nature of the structural proteins (not "membrane proteins," but things like cytoskeleton-cytoplasmic ground substance, spindle, centrosome-centrioles, nuclear matrix, etc.), with which lipids interact. Modifying an extremely complex system, the living substance, cholesterol participates in complexity, and must be investigated with subtlety. I suspect that the physiological meaning of cholesterol has to do with movement, stability, differentiation, memory, and sensitivity of the parts of the cells, that is, with everything physiological.

The functions of cholesterol parallel the functions of other sterols in plants and other types of organism. Its functions have been refined and extended with the development of other steroids, such as progesterone, as biological requirements have evolved, but cholesterol is still at the center of this system. To deliberately interfere with its synthesis, as contemporary medicine does, reveals a terrible arrogance.

Many participants in the cholesterol-lowering cult believe that they have succeeded in hijacking our science culture, but when the patents on another generation of their drugs have expired, the cult could begin to fade away.

Coconut Oil

Ray Peat's Newsletter, 2006

I have already discussed the many toxic effects of the unsaturated oils, and I have frequently mentioned that coconut oil doesn't have those toxic effects, though it does contain a small amount of the unsaturated oils. Many people have asked me to write something on coconut oil. I thought I might write a small book on it, but I realize that there are no suitable channels for distributing such a book—if the seed-oil industry can eliminate major corporate food products that have used coconut oil for a hundred years, they certainly have the power to prevent dealers from selling a book that would affect their market more seriously. For the present, I will just outline some of the virtues of coconut oil.

The unsaturated oils in some cooked foods become rancid in just a few hours, even at refrigerator temperatures, and are responsible for the stale taste of left-over foods. (Eating slightly stale food isn't particularly harmful, since the same oils, even when eaten absolutely fresh, will oxidize at a much higher rate once they are in the body, where they are heated and thoroughly mixed with an abundance of oxygen.) Coconut oil that has been kept at room temperature for a year has been tested for rancidity, and showed no evidence of it. Since we would expect the small percentage of unsaturated oils naturally contained in coconut oil to become rancid, it seems that the other (saturated) oils have an antioxidative effect: I suspect that the dilution keeps the unstable unsaturated fat molecules spatially separated from each other, so they can't interact in the destructive chain reactions that occur in other oils. To interrupt chain-reactions of oxidation is one of the functions of antioxidants, and it is possible that a sufficient quantity of coconut oil in the body has this function. It is well established that dietary coconut oil reduces our need for vitamin E, but I think its antioxidant role is more general than that, and that it has both direct and indirect antioxidant activities.

Coconut oil is unusually rich in short and medium chain fatty acids. Shorter chain length allows fatty acids to be metabolized without use of the carnitine transport system. Mildronate, which I discussed in an article on adaptogens, protects cells against stress partly by opposing the action of carnitine, and comparative studies showed that added carnitine had the opposite effect, promoting the oxidation of unsaturated fats

during stress, and increasing oxidative damage to cells. I suspect that a degree of saturation of the oxidative apparatus by short-chain fatty acids has a similar effect—that is, that these very soluble and mobile short-chain saturated fats have priority for oxidation, because they don't require carnitine transport into the mitochondrion, and that this will tend to inhibit oxidation of the unstable, peroxidizable unsaturated fatty acids.

When Albert Schweitzer operated his clinic in tropical Africa, he said it was many years before he saw any cases of cancer, and he believed that the appearance of cancer was caused by the change to the European type of diet. In the 1920s, German researchers showed that mice on a fat-free diet were practically free of cancer. Since then, many studies have demonstrated a very close association between consumption of unsaturated oils and the incidence of cancer.

Heart damage is easily produced in animals by feeding them linoleic acid; this "essential" fatty acid turned out to be the heart toxin in rapeseed oil. The addition of saturated fat to the experimental heart-toxic oil-rich diet protects against the damage to heart cells.

Immunosuppression was observed in patients who were being "nourished" by intravenous emulsions of "essential fatty acids," and as a result coconut oil is used as the basis for intravenous fat feeding, except in organ-transplant patients. For those patients, emulsions of unsaturated oils are used specifically for their immunosuppressive effects.

General aging, and especially aging of the brain, is increasingly seen as being closely associated with lipid peroxidation.

Several years ago I met an old couple, who were only a few years apart in age, but the wife looked many years younger than her doddering old husband. She was from the Philippines, and she remarked that she always had to cook two meals at the same time, because her husband couldn't adapt to her traditional food. Three times every day, she still prepared her food in coconut oil. Her apparent youth increased my interest in the effects of coconut oil.

In the 1960s, Hartroft and Porta gave an elegant argument for decreasing the ratio of unsaturated oil to saturated oil in the diet (and thus in the tissues). They showed that the "age pigment" is produced in proportion to the ratio of oxidants to antioxidants, multiplied by the ratio of unsaturated oils to saturated oils. More recently, a variety of studies have demonstrated that ultraviolet light induces peroxidation in

unsaturated fats, but not saturated fats, and that this occurs in the skin as well as *in vitro*. Rabbit experiments, and studies of humans, showed that the amount of unsaturated oil in the diet strongly affects the rate at which aged, wrinkled skin develops. The unsaturated fat in the skin is a major target for the aging and carcinogenic effects of ultraviolet light, though not necessarily the only one.

In the 1940s, farmers attempted to use cheap coconut oil for fattening their animals, but they found that it made them lean, active and hungry. For a few years, an antithyroid drug was found to make the livestock get fat while eating less food, but then it was found to be a strong carcinogen, and it also probably produced hypothyroidism in the people who ate the meat. By the late 1940s, it was found that the same antithyroid effect, causing animals to get fat without eating much food, could be achieved by using soy beans and corn as feed.

Later, an animal experiment fed diets that were low or high in total fat, and in different groups the fat was provided by pure coconut oil, or a pure unsaturated oil, or by various mixtures of the two oils. At the end of their lives, the animals' obesity increased directly in proportion to the ratio of unsaturated oil to coconut oil in their diet, and was not related to the total amount of fat they had consumed. That is, animals which ate just a little pure unsaturated oil were fat, and animals which ate a lot of coconut oil were lean.

In the 1930s, animals on a diet lacking the unsaturated fatty acids were found to be "hypermetabolic." Eating a "normal" diet, these animals were malnourished, and their skin condition was said to be caused by a "deficiency of essential fatty acids." But other researchers who were studying vitamin B_6 recognized the condition as a deficiency of that vitamin. They were able to cause the condition by feeding a fat-free diet, and to cure the condition by feeding a single B vitamin. The hypermetabolic animals simply needed a better diet than the "normal," fat-fed, cancer-prone animals did.

G. W. Crile and his wife found that the metabolic rate of people in Yucatan, where coconut is a staple food, averaged 25 % higher than that of people in the United States. In a hot climate, the adaptive tendency is to have a lower metabolic rate, so it is clear that some factor is more than offsetting this expected effect of high environmental temperatures. The people there are lean, and recently it has been observed that the

women there have none of the symptoms we commonly associate with the menopause.

By 1950, then, it was established that unsaturated fats suppress the metabolic rate, apparently creating hypothyroidism. Over the next few decades, the exact mechanisms of that metabolic damage were studied. Unsaturated fats damage the mitochondria, partly by suppressing the respiratory enzyme, and partly by causing generalized oxidative damage. The more unsaturated the oils are, the more specifically they suppress tissue response to thyroid hormone, and transport of the hormone on the thyroid transport protein.

Plants evolved a variety of toxins designed to protect themselves from "predators," such as grazing animals. Seeds contain a variety of toxins, that seem to be specific for mammalian enzymes, and the seed oils themselves function to block proteolytic digestive enzymes in the stomach. The thyroid hormone is formed in the gland by the action of a proteolytic enzyme, and the unsaturated oils also inhibit that enzyme. Similar proteolytic enzymes involved in clot removal and phagocytosis appear to be similarly inhibited by these oils.

Just as metabolism is "activated" by consumption of coconut oil, which prevents the inhibiting effect of unsaturated oils, other inhibited processes, such as clot removal and phagocytosis, will probably tend to be restored by continuing use of coconut oil.

Brain tissue is very rich in complex forms of fats. The experiment (around 1978) in which pregnant mice were given diets containing either coconut oil or unsaturated oil showed that brain development was superior in the young mice whose mothers ate coconut oil. Because coconut oil supports thyroid function, and thyroid governs brain development, including myelination, the result might simply reflect the difference between normal and hypothyroid individuals. However, in 1980, experimenters demonstrated that young rats fed milk containing soy oil incorporated the oil directly into their brain cells, and had structurally abnormal brain cells as a result.

Lipid peroxidation occurs during seizures, and antioxidants such as vitamin E have some anti-seizure activity. Currently, lipid peroxidation is being found to be involved in the nerve cell degeneration of Alzheimer's disease.

Various fractions of coconut oil are coming into use as "drugs," meaning that they are advertised as treatments for diseases. Butyric acid is

used to treat cancer, lauric and myristic acids to treat virus infections, and mixtures of medium-chain fats are sold for weight loss. Purification undoubtedly increases certain effects, and results in profitable products, but in the absence of more precise knowledge, I think the whole natural product, used as a regular food, is the best way to protect health. The shorter-chain fatty acids have strong, unpleasant odors; for a couple of days after I ate a small amount of a medium-chain triglyceride mixture, my skin oil emitted a rank, goaty smell. Some people don't seem to have that reaction, and the benefits might outweigh the stink, but these things just haven't been in use long enough to know whether they are safe.

We have to remember that the arguments made for aspartame, monosodium glutamate, aspartic acid, and tryptophan—that they are like the amino acids that make up natural proteins—are dangerously false. In the case of amino acids, balance is everything. Aspartic and glutamic acids promote seizures and cause brain damage, and are intimately involved in the process of stress-induced brain aging, and tryptophan by itself is carcinogenic. Treating any complex natural product as the drug industry does, as a raw material to be fractionated in the search for "drug" products, is risky, because the relevant knowledge isn't sought in the search for an association between a single chemical and a single disease.

While the toxic unsaturated paint-stock oils, especially safflower, soy, corn and linseed (flaxseed) oils, have been sold to the public precisely for their drug effects, all of their claimed benefits were false. When people become interested in coconut oil as a "health food," the huge seed-oil industry—operating through their shills—are going to attack it as an "unproved drug."

While components of coconut oil have been found to have remarkable physiological effects (as antihistamines, antiinfectives/antiseptics, promoters of immunity, glucocorticoid antagonist, nontoxic anticancer agents, for example), I think it is important to avoid making any such claims for the natural coconut oil, because it very easily could be banned from the import market as a "new drug" which isn't "approved by the FDA." We have already seen how money and propaganda from the soy oil industry eliminated long-established products from the U.S. market. I saw people lose weight stably when they had the habit of eating large amounts of tortilla chips fried in coconut oil, but those chips disappeared when their producers were pressured into switching to other oils, in spite

of the short shelf life that resulted in the need to add large amounts of preservatives. Oreo cookies, Ritz crackers, potato chip producers, and movie theater popcorn makers have experienced similar pressures.

The cholesterol-lowering fiasco for a long time centered on the ability of unsaturated oils to slightly lower serum cholesterol. For years, the mechanism of that action wasn't known, which should have suggested caution. Now, it seems that the effect is just one more toxic action, in which the liver defensively retains its cholesterol, rather than releasing it into the blood. Large scale human studies have provided overwhelming evidence that whenever drugs, including the unsaturated oils, were used to lower serum cholesterol, mortality increased, from a variety of causes including accidents, but mainly from cancer.

Since the 1930s, it has been clearly established that suppression of the thyroid raises serum cholesterol (while increasing mortality from infections, cancer, and heart disease), while restoring the thyroid hormone brings cholesterol down to normal. In this situation, however, thyroid isn't suppressing the synthesis of cholesterol, but rather is promoting its use to form hormones and bile salts. When the thyroid is functioning properly, the amount of cholesterol in the blood entering the ovary governs the amount of progesterone being produced by the ovary, and the same situation exists in all steroid-forming tissues, such as the adrenal glands and the brain. Progesterone and its precursor, pregnenolone, have a generalized protective function: antioxidant, anti-seizure, antitoxin, anti-spasm, anti-clot, anti-cancer, pro-memory, pro-myelination, pro-attention, etc. Any interference with the formation of cholesterol will interfere with all of these exceedingly important protective functions.

As far as the evidence goes, it suggests that coconut oil, added regularly to a balanced diet, lowers cholesterol to normal by promoting its conversion into pregnenolone. (The coconut family contains steroids that resemble pregnenolone, but these are probably mostly removed when the fresh oil is washed with water to remove the enzymes which would digest the oil.) Coconut-eating cultures in the tropics have consistently lower cholesterol than people in the U.S. Everyone that I know who uses coconut oil regularly happens to have cholesterol levels of about 160, while eating mainly cholesterol rich foods (eggs, milk, cheese, meat, shellfish). I encourage people to eat sweet fruits, rather than starches, if they want to increase their production of cholesterol, since fructose has that effect.

Many people see coconut oil in its hard, white state, and—as a result of their training watching television or going to medical school—associate it with the cholesterol-rich plaques in blood vessels. Those lesions in blood vessels are caused mostly by lipid peroxidation of unsaturated fats, and relate to stress, because adrenaline liberates fats from storage, and the lining of blood vessels is exposed to high concentrations of the blood-borne material. In the body, incidentally, the oil can't exist as a solid, since it liquefies at 76 °F. (Incidentally, the viscosity of complex materials isn't a simple matter of averaging the viscosity of its component materials; cholesterol and saturated fats sometimes lower the viscosity of cell components.)

Most of the images and metaphors relating to coconut oil and cholesterol that circulate in our culture are false and misleading. I offer a counter-image, which is metaphorical, but it is true in that it relates to lipid peroxidation, which is profoundly important in our bodies. After a bottle of safflower oil has been opened a few times, a few drops that get smeared onto the outside of the bottle begin to get very sticky, and hard to wash off. This property is why it is a valued base for paints and varnishes, but this varnish is chemically closely related to the age pigment that forms "liver spots" on the skin, and similar lesions in the brain, heart, blood vessels, lenses of the eyes, etc. The image of "hard, white saturated coconut oil" isn't relevant to the oil's biological action, but the image of "sticky varnish-like easily oxidized unsaturated seed oils" is highly relevant to their toxicity.

The ability of some of the medium chain saturated fatty acids to inhibit the liver's formation of fat very likely synergizes with the prothyroid effect, in allowing energy to be used, rather than stored. When fat isn't formed from carbohydrate, the sugar is available for use, or for storage as glycogen. Therefore, shifting from unsaturated fats in foods to coconut oil involves several anti-stress processes, reducing our need for the adrenal hormones. Decreased blood sugar is a basic signal for the release of adrenal hormones. Unsaturated oil tends to lower the blood sugar in at least three basic ways. It damages mitochondria, causing respiration to be uncoupled from energy production, meaning that fuel is burned without useful effect. It suppresses the activity of the respiratory enzyme (directly, and through its anti-thyroid actions), decreasing the respiratory production of energy. And it tends to direct carbohydrate into fat production, making both stress and obesity more probable. For

those of us who use coconut oil consistently, one of the most noticeable changes is the ability to go for several hours without eating, and to feel hungry without having symptoms of hypoglycemia.

One of the stylish ways to promote the use of unsaturated oils is to refer to their presence in "cell membranes," and to claim that they are essential for maintaining "membrane fluidity." As I have mentioned above, it is the ability of the unsaturated fats, and their breakdown products, to interfere with enzymes and transport proteins, which accounts for many of their toxic effects, so they definitely don't just harmlessly form "membranes." They probably bind to all proteins, and disrupt some of them, but for some reason their affinity for proteolytic and respiration-related enzymes is particularly obvious. (I think the chemistry of this association is going to give us some important insights into the nature of organisms.

Metchnikof's model that I have discussed elsewhere might give us a picture of how those factors relate in growth, physiology, and aging.) Unsaturated fats are slightly more water-soluble than fully saturated fats, and so they do have a greater tendency to concentrate at interfaces between water and fats or proteins, but there are relatively few places where these interfaces can be usefully and harmlessly occupied by unsaturated fats, and at a certain point, an excess becomes harmful. We don't want "membranes" forming where there shouldn't be membranes. The fluidity or viscosity of cell surfaces is an extremely complex subject, and the degree of viscosity has to be appropriate for the function of the cell. Interestingly, in some cells, such as the cells that line the air sacs of the lungs, cholesterol and one of the saturated fatty acids found in coconut oil can increase the fluidity of the cell surface.

In many cases, stressful conditions create structural disorder in cells. These influences have been called "chaotropic," or chaos-producing. In red blood cells, which have sometimes been wrongly described as "hemoglobin enclosed in a cell membrane," it has been known for a long time that lipid peroxidation of unsaturated fats weakens the cellular structure, causing the cells to be destroyed prematurely. Lipid peroxidation products are known to be "chaotropic," lowering the rigidity of regions of cells considered to be membranes. But the red blood cell is actually more like a sponge in structure, consisting of a "skeleton" of proteins, which (if not damaged by oxidation) can hold its shape, even when the hemoglobin has been removed. Oxidants damage the protein

structure, and it is this structural damage which in turn increases the "fluidity" of the associated fats.

So, it is probably true that in many cases the liquid unsaturated oils do increase "membrane fluidity," but it is now clear that in at least some of those cases the "fluidity" corresponds to the chaos of a damaged cell protein structure.[1]

Although I had stopped using the unsaturated seed oils years ago, and supposed that I wasn't heavily saturated with toxic unsaturated fat, when I first used coconut oil I saw an immediate response, that convinced me my metabolism was chronically inhibited by something that was easily alleviated by "dilution" or molecular competition. I had put a tablespoonful of coconut oil on some rice I had for supper, and half an hour later while I was reading, I noticed I was breathing more deeply than normal. I saw that my skin was pink, and I found that my pulse was faster than normal—about 98, I think. After an hour or two, my pulse and breathing returned to normal. Every day for a couple of weeks I noticed the same response while I was digesting a small amount of coconut oil, but gradually it didn't happen any more, and I increased my daily consumption of the oil to about an ounce. I kept eating the same foods as before (including a quart of ice cream every day), except that I added about 200 or 250 calories per day as coconut oil. Apparently the metabolic surges that happened at first were an indication that my body was compensating for an anti-thyroid substance by producing more thyroid hormone; when the coconut oil relieved the inhibition, I experienced a moment of slight hyperthyroidism, but after a time the inhibitor became less effective, and my body adjusted by producing slightly less thyroid hormone. But over the next few months, I saw that my weight was slowly and consistently decreasing. It had been steady at 185 pounds for 25 years, but over a period of six months it dropped to about 175 pounds. I found that eating more coconut oil lowered my weight another few pounds, and eating less caused it to increase.

The anti-obesity effect of coconut oil is clear in all of the animal studies, and in my friends who eat it regularly. It is now hard to get it in health food stores, since Hain stopped selling it. The Spectrum product looks and feels a little different to me, and I suppose the particular type of tree, region, and method of preparation can account for variations in the consistency and composition of the product. The unmodified natural

oil is called “76 °F melt,” since that is its natural melting temperature. One bottle from a health food store was labeled “natural coconut oil, 92 % unsaturated oil,” and it had the greasy consistency of old lard. I suspect that someone had confused palm oil (or something worse) with coconut oil, because it should be about 96 % saturated fatty acids.

Diabetes, Scleroderma, Oils and Hormones

Ray Peat's Newsletter, 2006

The basic argument: Stress and aging make cells less responsive in many ways by damaging their ability to produce energy and to adapt. The polyunsaturated fats are universally toxic to the energy producing system, and act as a "misleading signal" channeling cellular adaptation down certain self-defeating pathways. Diabetes is just one of the "terminal" diseases that can be caused by the polyunsaturated vegetable oils. Coconut oil, in diabetes as in other degenerative diseases, is highly protective.

When the oral contraceptive pill was new (Enovid), it was found to produce signs of diabetes, including decreased glucose tolerance. Spellacy and Carlson[1] suggested that an elevation of circulating free fatty acids might be responsible, and remarked that "Free fatty acids can block the Krebs cycle, with relative insulin action resistance resulting." "The potential danger of the oral contraceptives is one of prolonged pancreatic stimulation." Recent papers are reporting that the estrogen used to "treat menopause" causes an increase in free fatty acids. Spellacy and Carlson suggested that estrogen's effect was mediated by growth hormone, and that is now the consensus. Women are much more likely than men to develop diabetes.

Ephraim Racker observed that free unsaturated fatty acids inhibit mitochondrial respiration, and recent studies are finding that free linoleic and linolenic acids act as intracellular regulators, stimulating the protein kinase C (PKC) system, which is also stimulated by estrogen and the (cancer promoting) phorbol esters. They stimulate the cell while blocking the energy it needs to respond.

Scleroderma, or systemic sclerosis, is a supposedly mysterious condition in which tissues harden, with an excessive deposition of fibrous material. Besides hardening the skin, it can involve fibrosis of the heart and other organs, and can cause changes in blood vessels of the kidneys like those seen in some types of hypertension, and often involves Raynaud's phenomenon and osteoporosis of the fingers. (Silicone functions as an adjuvant, making exposure to irritants, solvents or infections more harmful. This seems to be the reason for the association between breast implants and scleroderma.) Another type of disease that involves

hardening of the skin is scleredema, in which the skin thickens with an accumulation of "mucin" between collagen bundles, and in which fibroblasts are overactive in producing collagen.[2] This condition is believed to often follow a "febrile illness" and is associated with diabetes. My interest in these conditions comes from my awareness that estrogen promotes collagen formation, and that changes in the connective tissue are deeply associated with the processes of stress and aging, following the ideas of Metchnikov and Selye.

Many people are still committed to the various old theories of diabetes, though a few are showing ways in which multiple causes can lead to diabetes. Increasingly, old age itself is seen to be "like diabetes,"[3] and the situation is ripe for a recentering of our understanding of diabetes around some of the general facts about aging and stress.

Diabetes mellitus, as named, refers to excessive urination and sugary urine, but it is now often diagnosed in people who neither urinate excessively nor pass glucose in the urine, on the basis of a high level of glucose in the blood. Many other signs (abnormal mucopolysaccharide metabolism with thickening of basement membranes, leakage of albumin through capillary walls and into the urine, a high level of free fatty acids in the blood, insensitivity of tissues to insulin, or reduced sensitivity of the beta cells to glucose) are considered diagnostic by some people, who believe that the worst aspects of the disease can be prevented if they can diagnose early and take preventive measures. This attitude derives largely from the genetic theory of causation, though it incorporates a belief that (environmental) intervention can ameliorate the course of the disease. When I wrote Nutrition for Women, I mentioned that the sudden appearance of diabetes in non-European Jews when they moved to Isreal made the genetic theory of diabetes untenable, and since then other studies have made the similar point that environmental factors seem crucial.[4] Many people are arguing for the racial/genetic theory of diabetes, but they are failing to consider some simple dietary factors, especially the high consumption of unsaturated seed oils and the combination of nutritional deficiencies and environmental stress.

I have known adults and children who were diagnosed as diabetic, and given insulin (and indoctrinated with the idea that they had a terminal degenerative disease) on the strength of a single test showing excessive glucose. When I taught at the naturopathic medical school in Portland, I tried to make it clear that "diabetes" (a term referring to

excessive urination) is a function, and that a high level of glucose in the blood or urine is also a function, and that the use of insulin should require a greater diagnostic justification than the use of aspirin for a headache does, because insulin use itself constitutes a serious health problem. (And we seldom hear the idea that "diabetes" might have a positive side,[5] for example that it reduces the symptoms of asthma,[6] which get worse when insulin is given. Normal pregnancy can be considered "diabetic" by some definitions based on blood sugar. I got interested in this when I talked to a healthy "diabetic" woman who had a two year old child whose IQ must have been over 200, judging by his spontaneous precocious hobbies. Old gynecologists told me that it was common knowledge that "diabetic" women had intellectually precocious children.)

When non-diabetic apes were given insulin treatments, they developed some of the same "complications of diabetes" that are seen in humans, and antibodies to insulin were found in their retinas, suggesting that some "complications of diabetes" were complications of insulin treatment. Patients were seldom well informed of the arguments against the use of insulin, but the justification for the new genetically engineered human insulin is precisely that it avoids immunological damage.

Insulin was introduced into medicine in the 1920s. According to the *Britannica Book of the Year* for 1947, page 265, "Mortality from diabetes in 1920 in the United States was 16.0 per 100,000, 14,062 deaths, but in 1944, it was 26.4 per 100,000, 34,948 deaths."

One of the theories of the cause of diabetes is that a virus damages the beta cells in the pancreas, and the main argument for that in the 1970s was that the onset of diabetes in children can often be dated to a time shortly after a severe viral infection. It is true that intense sickness and a high fever (and high doses of drugs given to treat the sickness) can cause very high levels of glucose in the blood, and even glucose in the urine, but this is a fairly well recognized consequence of stress. High doses of cortisone (prednisone, etc.) typically cause elevated glucose levels. Cushing's syndrome usually involves hyperglycemia. Normally, this is just a functional response to an excess of glucocorticoids, but studies in dogs suggested that intense and/or prolonged stress can damage the insulin-secreting cells in the pancreas. Dogs had half of their pancreas removed, to increase the burden put on the remaining tissue, and after a large dose of cortisone the dogs became (and remained) diabetic.

One of the problems associated with diabetes is the calcification of blood vessels, though now there is more emphasis on fatty degeneration. Other blood vessel problems include hypertension, and poor circulation in general, leading to gangrene of the feet, impotence, and degeneration of the retina. In muscles, and probably in other tissues of diabetics, capillaries are more widely spaced, as if the basal oxidative requirement were lower than normal. However, mitochondria contain more respiratory enzymes, as if to partly compensate for the poor delivery of oxygen to the cells. Osteoporosis or osteopenia is a common complication of diabetes, and seems to be associated with the calcification of soft tissues.

F. Z. Meerson's description of the stress-injured heart is very similar to the general changes that occur in chronic diabetes. He found that the stressed heart becomes rigid and unable to contract completely, or to relax completely. Excess calcium enters cells, and fatty acids are mobilized both locally and systemically, and both of these tend to damage the mitochondria. In diabetes, fatty acids are mobilized and oxidized instead of glucose, and calcium enters cells, increasing their rigidity and preventing relaxation of muscles in blood vessels. (I'm not sure whether it is relevant to cell physiology, but the presence of an excess of free unsaturated fatty acids, and of calcium, in cells makes me think of the insoluble soap that these substances form in other situations, including the intestine. It seems that this could form a harmful deposit in cells, blocking many metabolic processes.)

For many years, histologists have observed that calcium and iron tend to be deposited together in "devitalized" tissues. Now we know that cell death from a great variety of causes involves the cell's absorption of increased amounts of calcium. Simply the lack of energy increases the amount of calcium in a cell, and stimulation or excitation does the same, creating or exaggerating a deficiency of energy. In low thyroid people, many (if not all) tissues are very easily damaged. Since glucose is needed by liver cells to produce the active (T_3) form of thyroid, diabetes almost by definition will produce hypothyroidism, since in diabetes glucose can't be absorbed efficiently by cells.

In the form of cell damage caused by the "excitotoxins," glutamic and aspartic acids, the damage seems to require both stimulation, and difficulty in maintaining adequate energy production. This combination leads to both calcium uptake and lipid peroxidation. When cells are de-energized, they tend to activate iron by chemical reduction, producing

lipid peroxidation. This could explain the presence of chemically active iron, but an actual increase in the iron concentration suggests that there has been prolonged injury (oxidative stress) to the cell, with increased production of the heme group, which binds iron.

Hans Selye found that he could produce scleroderma (hardening and calcification of the skin) in rats by giving them a toxic dose of a heavy metal, and then irritating the skin a little by plucking hair. Iron is now tending to be recognized as a factor in inflammation. Vitamin E was able to prevent the development of scleroderma under Selye's experimental conditions, suggesting that the irritation allowed the heavy metal to cause oxidative damage to the skin. Selye found other ways to cause calcification of tissues, including the walls of arteries, but he directed most of his attention to the role of "pro-inflammatory" hormones. A decreased blood supply was often used to predispose an organ to calcification. In diabetes, a characteristic feature is that the blood supply is relatively remote from cells in muscle and skin, so the oxygen and nutrients have to diffuse farther than in normal individuals, and the ATP level of cells is characteristically lower than normal. In blood cells, both red[7] and white cells are probably more rigid in diabetes, because of lower ATP production, and higher intracellular calcium and sodium.

Magnesium in the cell is largely associated with ATP, as the complex Mg-ATP. When ATP is "used" or converted to ADP, this lower-energy substance associates with calcium, as Ca-ADP. In a hypothyroid state, the energy charge can be depleted by stress, causing cells to lose magnesium. ATP is less stable when it isn't complexed with magnesium, so the stress-induced loss of magnesium makes the cell more susceptible to stress, by acting as a chronic background stimulation, forcing the cell to replace the ATP which is lost because of its instability. In this state, the cell takes up an excess of calcium.

The picture that I think explains many of the features of diabetes is that an energy deficit produces an alarm state, causing increased production of adrenalin and cortisol. Adrenalin mobilizes fat from storage, and the free fatty acids create a chronic problem involving 1) blocked ATP production, 2) activation of the protein kinase C system (increasing tension in blood vessels), 3) inhibition of thyroid function with its energetic, hormonal, and tissue-structure consequences, 4) availability of fats for prostaglandin synthesis, and 5) possibly a direct effect on clot dissolving, besides the PAI-1 (plasminogen activator inhibitor)

effect seen in diabetes.[8–10] (Estrogen has many pro-clotting effects, and one of them is a decreased activity of vascular plasminogen activator.[11] Estrogen also promotes thromboembolism by increasing clotting factor IX in the blood.[12])

Increased entry of calcium into cells is complexly related to increased exposure to unsaturated fatty acids, decreased energy, and lipid peroxidation. Osteoporosis, calcification of soft tissues and high blood pressure are promoted by multiple stresses, hypothyroidism, and magnesium deficiency. The particular direction a disease takes—diabetes, scleroderma, lupus, Alzheimer's, stroke, etc.—probably results from the balance between resources and demands within a particular organ or system. Calcium overload of cells can't be avoided by avoiding dietary calcium, because the bones provide a reservoir from which calcium is easily drawn during stress. (In fact, the reason calcium can temporarily help prevent muscle cramps seems to be that it makes magnesium more available to the muscles.)

If we want to stop a disease that involves abnormal calcification or contraction of muscle,[13] we can increase our consumption of magnesium, and to cause cells to absorb and retain the magnesium, we can increase our thyroid function. The use of coconut oil provides energy to stabilize blood sugar while protecting mitochondria and the thyroid system from the harmful effects of unsaturated fats.

In 1947, B. A. Houssay found that a diet based on sugar as a source of energy was more protective against diabetes than a diet based on lard, while the most protective diet was based on coconut oil. Lard reflects the pigs' diet, and is usually extremely unsaturated, especially since it became standard to fatten them on soybeans and corn. Essentially, his study seems to show that unsaturated (pork) fat permits diabetes to develop, sugar is slightly protective, and coconut oil is very protective against the form of diabetes caused by a poison.

At the same time, A. Lazarow was demonstrating that a low protein diet made animals more sensitive to diabetes, and that cysteine, glutathione, and thioglycolic acid (antioxidants) are protective against diabetes. The chelator of metals, BAL (British anti-lewisite), was also found to protect against diabetes.

Taken together, those studies suggest that the oxidizable unsaturated fats are involved in the process of producing diabetes. At the same time, other studies were showing that the unsaturated oils suppress the

thyroid, and that coconut oil increases the metabolic rate, apparently by normalizing thyroid function. Hypothyroidism is known to include deposition of mucopolysaccharides in tissues, increased permeability of capillaries with leakage of albumin out of the blood, elevated adrenalin which can lead to increased production of cortisol, decreased testosterone production, high risk of heart and circulatory disease, including a tendency to ulceration of the extremities, and osteoporosis, all of which are recognized "complications of diabetes." Broda Barnes gave all of his diabetic patients a thyroid supplement, and found that none of them developed the expected complications of diabetes.

Recently, a high safflower oil diet was found to cause diabetes,[14] and obesity itself is thought to be a factor in developing diabetes. The hormone patterns associated with obesity can be seen as either cause or effect of the obesity (or both cause and effect), since, for example, low thyroid can increase both estrogen and cortisol, which support the formation of fat, and the fat cells can become a chronic source of estrogen synthesis.

On a diet lacking the "essential" unsaturated fatty acids,Benhamou[15] found that nonobese diabetic mice didn't develop diabetes, that is, the unsaturated fats themselves, without obesity, are sufficient to cause diabetes.[16–18]

Estrogen and the polyunsaturated fatty acids (PUFA), linoleic and linolenic acid, alike activate the protein kinase C (PKC) system of cellular activation. Many of the functions of PUFA are similar to the functions of estrogen (e.g., antagonism to thyroid function, promotion of age pigment/lipofuscin), so this information showing that they both act similarly on the same basic regulatory pathway is important. Estrogen increases secretion of growth hormone (GH; it's closely associated with prolactin, also increased by estrogen), and GH causes an increase in free fatty acids in the blood. Estrogen promotes iron retention, so it sets the stage for oxidative stress. At least in some systems, both estrogen and PUFA promote the entry of calcium into the cell.

In diabetes, there is a generalized excess activation of the PKC system. The starch-based diet, emphasizing grains, beans, nuts, and vegetables, has been promoted with a variety of justifications. When people are urged to reduce their fat and sugar consumption, they are told to eat more starch. Starch stimulates the appetite, promotes fat synthesis by stimulating insulin secretion, and sometimes increases the growth of

bacteria that produce toxins. It is often associated with allergens, and according to Gerhard Volkheimer, whole starch grains can be "persorbed" from the intestine directly into the blood stream where they may block arterioles, causing widely distributed nests of cell-death. I have heard dietitians urge the use of "complex carbohydrates" (starch) instead of sugar. In the first physiology lab I took, we fed rats a large blob of moist cornstarch with a stomach tube, and then after waiting a few minutes, were told to dissect the rat to find out "how far the starch had gone." In such a short time, we were surprised to find that not a trace of the starch could be found. The professor's purpose was to impress us with the rapidity with which starch is digested and absorbed. Various studies have demonstrated that starch (composed of pure glucose) raises blood glucose more quickly than sucrose (half fructose, half glucose) does. The sudden increase of blood glucose is sometimes thought to contribute to the development of diabetes, but if it does, it is probably mediated by fat metabolism and the hormones other than just insulin.

Brewer's yeast has been used successfully to treat diabetes. In the l930s, my father had severe diabetes, but after a few weeks of living on brewer's yeast, he recovered and never had any further evidence of diabetes. Besides its high B-vitamin and protein content, yeast is an unusual food that should be sparingly used, because of its high phosphorous/calcium ratio, high potassium to sodium ratio, and high estrogen content. The insulin-producing beta cells of the pancreas have estrogen receptors, but I don't know of any new research investigating this aspect of yeast therapy. In rabbit studies, diabetes produced by alloxan poisoning, which kills the beta cells, was cured by DHEA treatment, and beta cells were found to have regenerated in the pancreatic islets.

I think the basic anti-aging diet is also the best diet for prevention and treatment of diabetes, scleroderma, and the various "connective tissue diseases." This would emphasize high protein, low unsaturated fats, low iron, and high antioxidant consumption, with a moderate or low starch consumption. In practice, this means that a major part of the diet should be milk, cheese, eggs, shellfish, fruits and coconut oil, with vitamin E and salt as the safest supplements. It should be remembered that amino acids, especially in eggs, stimulate insulin secretion, and that this can cause hypoglycemia, which in turn causes cortisol secretion. Eating fruit (or other carbohydrate), coconut oil, and salt at the same

meal will decrease this effect of the protein. Magnesium carbonate and epsom salts can also be useful and safe supplements, except when the synthetic material causes an allergic bowel reaction.

Although I started this newsletter with the thought of discussing the Mead acids—the unsaturated (n-9) fats that are formed under certain conditions, especially when the dietary polyunsaturated fatty acids are "deficient"—and their prostaglandin derivatives as a distinct anti-stress, anti-aging system, the loss of which makes us highly susceptible to injury, I will save that argument for a future time, leaving this newsletter as an addition to the view that an excess of the polyunsaturated fats is central to the development of degenerative diseases: Cancer, heart disease, arthritis, immunodeficiency, diabetes, hypertension, osteoporosis, connective tissue disease, and calcification.

Eclampsia in the Real Organism

A Paradigm of General Distress Applicable in Infants, Adults, etc.

Ray Peat's Newsletter, 2007

To prevent the appropriation and abuse of our language by academic and professional cliques, I like to recall my grandparents' speech. When my grandmother spoke of eclampsia, the word was still normal English, that reflected the Greek root meaning, "shining out," referring to the visual effects that are often prodromal to seizures. The word was most often used in relation to pregnancy, but it could also be applied to similar seizures in young children. The word is the sort that might have been coined by a person who had experienced the condition, but the experience of seeing hallucinatory lights is seldom mentioned in the professional discussion of "eclampsia and preeclampsia."

Metaphoric thinking—using comparisons, models, or examples—is our natural way of gaining new understanding. Ordinary language, and culture, grow when insightful comparisons are generally adopted, extending the meaning of old categories. Although the free growth of insight and understanding might be the basic law of language and culture, we have no institutions that are amenable to that principle of free development of understanding. Institutions devoted to power and control are naturally hostile to the free development of ideas.

Among physicians, toxemia (meaning poisons in the blood) has been used synonymously with preeclampsia, to refer to the syndrome in pregnant women of high blood pressure, albumin in the urine, and edema, sometimes ending in convulsions. Eclampsia is reserved for the convulsions themselves, and is restricted to the convulsions which follow preeclampsia, when there is "no other reason" for the seizure such as "epilepsy" or cerebral hemorrhage. Sometimes it is momentarily convenient to use medical terms, but we should never forget the quantity of outrageous ignorance that is attached to so many technical words when they suggest the identity of unlike things, and when they partition and isolate things which have meaning only as part of a process. Misleading terminology has certainly played an important role in retarding the understanding of the problems of pregnancy.

In 1974, when I decided to write Nutrition for Women, I was motivated by the awful treatment I saw women receiving, especially during

pregnancy, from physicians and dietitians. Despite the research of people like the Shutes and the Biskinds, there were still "educated" and influential people who said that the mother's diet had no influence on the baby. (That strange attitude affects many aspects of behavior and opinion.)

How can people believe that the mother's diet has no effect on the baby's health? Textbooks used to talk about the "insulated" fetus, which would get sufficient nutrients from the mother's body even if she were starving. To "prove" the doctrine, it was pointed out that the fetus gets enough iron to make blood even when the mother is anemic. In the last few years, the recognition that smoking, drinking, and using other drugs can harm the baby has helped to break down the doctrine of "insulation," but there is still not a medical culture in which the effects of diet on the physiology of pregnancy are appreciated. This is because of a mistaken idea about the nature of the organism and its development. "Genes make the organism," according to this doctrine, and if there are congenital defects in the baby, the genes are responsible. A simple sort of causality flows from the genes to the finished organism, according to that idea. It was taught that if "the genes" are really bad, the defective baby can make the mother sick, and she contributed to the baby's bad genes. The idea isn't completely illogical, but it isn't based on reality, and it is demonstrably false. (Race, age and parity have no effect on incidence of cerebral palsy; low birth weight and complications of pregnancy are associated with it.[1])

Although Sigmund Freud sensibly argued in 1897 that it was more reasonable to think that an infant's cerebral palsy was caused by the same factors that caused the mother's sickness, than to think that the baby's cerebral palsy caused maternal sickness and premature labor, more than 50 years later people were still taking seriously the idea that cerebral palsy might cause maternal complications and prematurity.[2]

Medical textbooks and articles still commonly list the conditions that are associated with eclampsia: Very young and very old mothers, a first pregnancy or a great number of previous pregnancies, diabetes, twins, obesity, excessive weight gain, and kidney disease. Some authors, observing the high incidence of eclampsia in the deep South, among Blacks and on American Indian reservations, have suggested that it is a genetic disease because it "runs in families." If poverty and malnutrition are also seen to "run in families," some of these authors have argued

that the bad genes which cause birth defects also cause eclampsia and poverty. (L. C. Chesley, et al.,[3] reported that women whose mothers suffered eclampsia during their gestation were likely to have eclampsia themselves. Some "researchers" have concluded that eclampsia is good, because many of the babies die, eliminating the "genes" for eclampsia and poverty.)† Any sensible farmer knows that pregnant animals must have good food if they are to successfully bear healthy young, but of course those farmers don't have a sophisticated knowledge of genetics.

The inclusion of obesity and "excessive weight gain" among the conditions associated with eclampsia has distracted most physicians from the fact that malnutrition is the basic cause of eclampsia. The pathologist who, knowing nothing about a woman's diet, writes in his autopsy report that the subject is "a well nourished" pregnant woman, reflects a medical culture which chooses to reduce "nutritional adequacy" to a matter of gross body weight. The attempt to restrict weight gain in pregnancy has expanded the problem of eclampsia beyond its association with poverty, into the more affluent classes.

Freud wasn't the first physician who grasped the idea that the baby's health depends on the mother's, and that her health depends on good nutrition. Between 1834 and 1843, John C. W. Lever, M.D., discovered that 9 out of 10 eclamptic women had protein in their urine. He described an eclamptic woman who bore a premature, low-weight baby, as having "…been living in a state of most abject penury for two or three months, subsisting for days on a single meal of bread and tea. Her face and body were covered with cachectic sores."[4] S. S. Rosenstein observed that eclampsia was preceded by changes in the serum.[5] L. A. A. Charpentier specifically documented low serum albumin as a cause of eclampsia.[6] Robert Ross, M.D., documented the role of malnutrition as the cause of proteinuria and eclampsia.[7]

In outline, we can visualize a chain of causality beginning with a diet deficient in protein, impairing liver function, producing inability to store glycogen, to inactivate estrogen and insulin, and to activate thyroid. Low protein and high estrogen cause increased tendency of the blood to clot. High estrogen destroys the liver's ability to produce albumin.[8] Low thyroid causes sodium to be lost. The loss of sodium albuminate causes tissue edema, while the blood volume is decreased. Decreased blood volume and hemoconcentration (red cells form a larger fraction of the blood) impair the circulation. Blood pressure increases. Blood sugar

becomes unstable, cortisol rises, increasing the likelihood of premature labor. High estrogen, hypoglycemia, viscous blood, increased tendency of the blood to clot cause seizures. Women who die from eclampsia often have extensive intravascular clotting, and sometimes the brain and liver show evidence of earlier damage, probably from clots that have been cleared. (Sometimes prolonged clotting consumes fibrinogen, causing inability to clot, and a tendency to hemorrhage.)[9] (See also: sodium decrease,[10] viscosity,[11] clotting,[12,13] progesterone decrease.[10,14])

But the simple chain of causality has many lines of feedback, exacerbating the problem, and the nutritional problem is usually worse than a simple protein deficiency. B vitamin deficiencies alone are enough to cause the liver's underactivity, and to cause estrogen dominance, and a simple vitamin A deficiency causes an inability to use protein efficiently or to make progesterone, and in itself mimics some of the effects of estrogen.

Anything that causes a thyroid deficiency will make the problem worse. Thyroid therapy alone has had spectacular success in treating and preventing eclampsia. (H. O. Nicholson, 1904, cited in Dieckman's *Toxemias of Pregnancy*, 1952; 1929, Barczi, of Budapest; Broda Barnes, who prescribed thyroid as needed, delivered more than 2,000 babies and never had a case of pre-eclampsia, though statistically 100 would have been expected.)

The clotting which sometimes kills women, can, if it is not so extensive, cause spotty brain damage, similar to that seen in "multiple sclerosis," or it can occur in the liver, or other organ, or in the placenta, or in the fetus, especially in its brain and liver. Some cases of supposed "post-partum psychosis" have been the result of multiple strokes. When large clots occur in the liver or placenta, the fibrinogen which has been providing the fibrin for disseminated intravascular coagulation can appear to be consumed faster than it is produced by the liver. I think its disappearance may sometimes be the result of the liver's diminished blood supply, rather than the "consumption" which is the way this situation is usually explained. It is at this point that hemorrhages, rather than clots, become the problem. The undernourished liver can produce seizures in a variety of ways—clots, hemorrhages, hypoglycemia, and brain edema, for example, so eclampsia needn't be so carefully discriminated from "the other causes of seizures."

Because I had migraines as a child, I was interested in their cause. Eating certain foods, or skipping meals, seemed to be involved, but I noticed that women often had migraines premenstrually. Epilepsy too, I learned, often occurred premenstrually.

In my experience of migraine, nausea and pain followed the visual signs, which consisted of a variable progression of blind spots and lights. When I eventually learned that I could stop the progression of symptoms by quickly eating a quart of ice cream, I saw that my insight could be applied to other situations in which similar visual events played a role, especially "eclampsia" and "epilepsy." For example, a woman who was 6 months pregnant called me around 10 o'clock one morning, to say that she had gone blind, and was alone in her country house. She said she had just eaten breakfast around 9 AM, and wasn't hungry, but I knew that the 6 month fetus has a great need for glucose, so I urged her to eat some fruit. She called me 15 minutes later to report that she had eaten a banana, and her vision had returned.

Early in pregnancy, "morning sickness" is a common problem, and it is seldom thought to have anything to do with eclampsia, because of the traditional medical idea that the fetus "causes" eclampsia, and in the first couple of months of pregnancy the conceptus is very small. But salty carbohydrate (soda crackers, typically) is the standard remedy for morning sickness. Some women have "morning sickness" premenstrually, and it (like the nausea of migraine) is eased by salt and carbohydrate. X-ray studies have demonstrated that there are spasms of the small intestine (near the bile duct) associated with estrogen-induced nausea.

Hypoglycemia is just one of the problems that develops when the liver malfunctions, but it is so important that orange juice or Coca Cola or ice cream can provide tremendous relief from symptoms. Sodium (orange juice and Pepsi provide some) helps to absorb the sugar, and—more basically—is essential for helping to restore the blood volume. Pepsi has been recommended by the World Health Organization for the rehydration of babies with diarrhea, in whom hypovolemia (thickening of the blood from loss of water) is also a problem.

The problem of refeeding starving people has many features in common with the problem of correcting the liver malfunction and hormone imbalances which follow prolonged malnutrition of a milder sort. The use of the highest quality protein (egg yolk or potato juice, or at least milk or meat) is important, but the supplementation of thyroid containing T_3

is often necessary. Intravenous albumin, hypertonic solutions of glucose and sodium, and magnesium in an effective form should be helpful (magnesium sulfate injected intramuscularly is the traditional treatment for eclampsia, since it is quickly effective in stopping convulsions). While the sodium helps to restore blood volume and to regulate glucose, under some circumstances (high aldosterone) it helps to retain magnesium; aldosterone is not necessarily high during eclampsia. Triiodothyronine directly promotes cellular absorption of magnesium. Hypertonic glucose with minerals is known to decrease the destruction of protein during stress.[15]

Katherina Dalton observed that her patients who suffered from PMS (and were benefitted by progesterone treatment) were likely to develop "toxemia" when they became pregnant, and to have problems at the time of menopause. In these women, it is common for "menstruation" to continue on the normal cycle during the first several months of pregnancy. This cyclic bleeding seems to represent times of an increased ratio of estrogen to progesterone, and during such periods of cyclic bleeding the risk of miscarriage is high. Researchers found that a single injection of progesterone could sometimes eliminate the signs of toxemia for the remainder of the pregnancy. Katherina Dalton, who continued to give her patients progesterone throughout pregnancy, later learned that the babies treated in this way were remarkably healthy and bright, while the average baby delivered after a "toxemic" pregnancy has an IQ of only 85.

Marian Diamond's work with rats clearly showed that increased exposure to estrogen during pregnancy reduced the size of the cerebral cortex and the animals' ability to learn, while progesterone increased the brain size and intelligence. Zamenhof's studies suggested that these hormones probably have their effects largely through their actions on glucose, though they also affect the availability of oxygen in the same way, and have a variety of direct effects on brain cells that would operate toward the same end.

If Katherina Dalton's patients' IQs averaged 130, instead of the expected 85, the potential social effects of proper health care during pregnancy are enormous.

But there is evidence that healthy gestation affects more than just the IQ. Strength of character, ability to reason abstractly, and the absence of physical defects, for example, are strongly associated with weight at birth.

Government studies and Social Security statistics suggest the size of the problem. The National Institute of Neurological Diseases and Stroke found that birth weight was directly related to IQ at age four, and that up to half of all children who were underweight at birth have an IQ under 70.[16] According to standard definitions, about 8 % of babies in the U.S. have low birth weight.

Among people receiving Social Security income because of disability that existed at the age of 18, 75 % were disabled before birth. In 94 % of these cases, the abnormality was neurological.[17]

A study of 8 to 10-year-old children found that abstract verbal reasoning and perceptual/motor integration are more closely related to birth weight than they are to IQ.[18]

National nutritional data show that in the U.S. the development of at least a million babies a year is "substantially compromised" by prenatal malnutrition. Miscarriages, which are also causally related to poor nutrition, occur at a rate of a few hundred thousand per year.[19]

When a muscle is fatigued, it swells, taking up sodium and water, and it is likely to become sore. Energy depletion causes any cell to take up water and sodium, and to lose potassium. An abnormal excess of potassium in the blood, especially when sodium is low, affects nerve, muscle, and secretory cells; a high level of potassium can stop the heart, for example. Cellular energy can be depleted by a combination of work, insufficient food or oxygen, or a deficiency of the hormones needed for energy production. When the swelling happens suddenly, the movement of water and sodium from the blood plasma into cells decreases the volume of blood, while the quantity of red cells remains the same, making the blood more viscous.

During the night, as adrenalin, cortisol, and other stress hormones rise, our blood becomes more viscous and clots more easily. In rats, it has been found that the concentration of serum proteins increases significantly during the night, presumably because water is moving out of the circulatory system. Even moderate stress causes some loss of water from the blood.

If a person is malnourished, a moderate stress can overcome the body's regulatory capacity. If tissue damage is extreme, or blood loss is great, even a healthy person experiences hypovolemia and shock.

C.A. Crenshaw, who was a member of the trauma team at Parkland Hospital in Dallas that worked on Kennedy and Oswald, had been in-

volved in research with G. T. Shires on traumatic shock. In his words, "we made medical history by discovering that death from hemorrhagic shock (blood loss) can be due primarily to the body's adjunctive depletion of internal salt water into the cells." (Shires' work involved isotopes of sodium to show that sodium seems to be taken up by cells during shock.)

According to Crenshaw, "Oswald did not die from damaged internal organs. He died from the chemical imbalances of hemorrhagic shock. From the time he was shot…until the moment fluids were introduced into the body…" (19 min) "there was very little blood circulating in Oswald's body. As a result, he was not getting oxygen, and waste built up in his cells. Then, when the fluids were started, the collection of waste from the cells was dumped into the bloodstream, suddenly increasing the acid level, and delivering these impurities to his heart. When the contaminated blood reached the heart, it went into arrest…" The "waste" he refers to includes potassium and lactic acid. Crenshaw advocates the use of Ringer's lactate to replace some of the lost fluid. Since the blood already contains a large amount of lactate because the body is unable to consume it, this doesn't seem reasonable. I think a hypertonic version of Locke's solution, containing glucose and sodium bicarbonate as well as sodium chloride, would be better, though I think the potassium should be omitted too, and extra magnesium would seem desirable. Triiodothyronine, I suspect, would help tremendously to deal with the problems of shock, causing potassium, magnesium, and phosphate to move back into cells, and sodium to move out, helping to restore blood volume and reduce the wasteful conversion of glucose to lactic acid.

Albumin has been used therapeutically in preeclampsia,[20] to restore blood volume. Synthetic polymers with similar osmotic properties are sometimes used in shock, and might also be useful in eclampsia, but simply eating extra protein quickly restores blood albumin. For example, in a group of women who were in their seventh month of pregnancy, the normal women's serum osmotic pressure was 247 mm ()water, that of the women with nonconvulsive toxemia was 215 mm, and in the women with eclampsia, the albumin and osmotic pressure were lowest, with a pressure of 175 mm. In the eighth month, the toxemic women who ate 260 g of protein daily had a 7 % increase in osmotic pressure, and a group who ate 20 g had a decline of 9 %.[21] In a group of preeclamptics, plasma volume was 39 % below that of normal pregnant women.

If the physiology of shock has some relevance for eclampsia, so does the physiology of heart failure, since Meerson has shown that it is a consequence of uncompensated stress. The failing heart shifts from mainly glucose oxidation to the inefficient use of fatty acids, which are mobilized during stress, and with its decreased energy supply, it is unable to beat efficiently, since it remains in a partly contracted state. Estrogen (which is increased in men who have had heart attacks) is another factor which decreases the heart's stroke volume, and estrogen is closely associated with the physiology of the free unsaturated fatty acids. The partly contracted state of the heart is effectively a continuation of the partly contracted state of the blood vessels that causes the hypertension, and reduced tissue perfusion seen in shock and eclampsia. Since shock can be seen as a generalized inflammatory state, and since aspirin has been helpful in protecting against heart disease, it's reasonable that aspirin has been tried as a treatment in pre-eclampsia. It seems to protect the fetus against intrauterine growth retardation, an effect that I think relates to aspirin's ability to protect in several ways against excesses of unsaturated fatty acids and of estrogen. But, since aspirin can interfere with blood clotting, its use around the time of childbirth can be risky, and it is best to correct the problem early enough that aspirin isn't needed.

Besides protein deficiency and other nutritional deficiencies, excess estrogen and low thyroid can also limit the liver's ability to produce albumin. Hypovolemia reduces liver function, and (like hepatic infarcts) will reduce its ability to maintain albumin production.

The studies which have found that hospitalized patients with the lowest albumin are the least likely to survive suggest that the hypovolemia resulting from hepatic inefficiency is a problem of general importance, and that it probably relates to the multiple organ failure which is an extremely common form of death among hospitalized patients. A diet low in sodium and protein probably kills many more people than has been documented. If old age is commonly a hypovolemic condition, then the common salt restriction for old-age hypertension is just as irrational as is salt-restriction in pregnancy or in shock. Thyroid (T_3), glucose, sodium, magnesium and protein should be considered in any state in

which weakened homeostatic control of the composition of plasma is evident.

† Although Konrad Lorenz (who later received the Nobel Prize) was the architect of the Nazi's policy of "racial hygiene" (extermination of those with unwanted physical, cultural, or political traits which were supposedly determined by "genes") he took his ideas from the leading U.S. geneticists, whose works were published in the main genetics journals. Following the Nazis' defeat, some of these journals were renamed, and the materials on eugenics were often removed from libraries, so that a new historical resume could be presented by the profession.

Epilepsy and Progesterone

Ray Peat's Newsletter, 2006

THE length of the life-span, and of the period of youth or immaturity, is closely associated with the size of the brain, and the brain has a very high rate of metabolism. When something interferes with this very high metabolic rate, the consequences may be instantaneous, or developmental, or chronic and degenerative, or even transgenerational. The issue of epilepsy centers on questions of brain metabolism, and so it has all of those dimensions.

As I discuss the mechanisms known to predispose a person to epilepsy, I will emphasize the centrality of oxidative energy production, and show how "stroke," "stress," "hyperactivity," "dementia," and other brain syndromes are related to "epilepsy." (Similar processes are being studied in the heart and other tissues; eventually, we might have a general language that will make it easier to understand the parallels in the various kinds of "seizure" in any organ.)

As an old term, "epilepsy" has acquired a burden of pseudoscientific ideas, covering old superstitions with an overlay of new superstitions. (Hereditary epilepsy has been discussed in countless textbooks and medical journals, but I think a much better case could be made for the inheritance of a tendency to offer stupid genetic explanations.) "Hereditary epilepsy" and "idiopathic epilepsy" are seriously pathogenic terms; "brain scar" sometimes has a factual basis, but most often the term is an evasion of understanding.

As long as we realize that the essential meaning of the word is "something that grabs you," "epilepsy" is a convenient way to refer to a cluster of convulsive states, fainting spells, night-terrors and nightmares, and strange sensations.

Seizures can be caused by lack of glucose, lack of oxygen, vitamin B_6 deficiency, and magnesium deficiency. They are more likely to occur during the night, during puberty, premenstrually, during pregnancy, during the first year of life, and can be triggered by hyperventilation, running, strong emotions, or unusual sensory stimulation. Water retention and low sodium increase susceptibility to seizures. When I was in high school, our dog found and ate a pint of bacon grease, and shortly afterward had a convulsive seizure. I knew of veterinarians who treated

seizures in dogs with a vermifuge, so it seemed obvious that a metabolic disturbance, especially if combined with intestinal irritation, could cause fits.

It was undoubtedly such observations that led some physicians to advocate removal of the colon as treatment for epilepsy. Pregnancy and the menstrual cycle have been recognized as having something to do with seizures, but when seizures occurred only during pregnancy, they were classified as nonepileptic, and when they had a clear premenstrual occurrence, they were likely to be classified as "hysterical fits," to be treated with punishment.

It has been observed that all "recognized" anti-seizure drugs are teratogenic, and women who are taking such drugs are told that pregnancy might kill them if they stop the drug, but that their babies will have a greatly increased risk of birth defects if they take the drugs during pregnancy. This is why a better understanding of epilepsy is very important. Old therapies are mainly important for the insight they can give into the nature of the physiological problem. Some of the well established clinical-laboratory observations[1,2] give strong hints as to the physiological problem, for example, low albumin, high prealbumin, low magnesium and high calcium all suggest hypothyroidism. (Problems with the bowel, liver, and sex hormones are highly associated with hypothyroidism, both as causes and as effects.) Water retention was so clearly involved in seizures that increased water intake was used as a diagnostic procedure. (R. Grinker) Unfortunately, animal experiments showed that water intoxication increased susceptibility to seizures even in normal individuals. Low sodium content in the body fluids also predisposed to seizures, so that someone with hyponatremia (low blood sodium) would be more susceptible to induction of a seizure by excessive water intake. (Excessive water uptake is still recognized as a factor in seizures, but now it is seen as part of a complex process, involving energy, hormones, and transmitter substances. E.g., Kempski; Chan.)

Hypothyroid people tend to lose sodium easily, and unopposed estrogen increases water retention, without an equivalent sodium retention, so low thyroid, high estrogen people have two of the conditions (edema and hyponatremia) known to predispose to seizures. Another outstanding feature of seizures of various sorts is that they are most likely to occur at night, especially in the early pre-dawn hours. Low blood sugar

and high adrenalin predominate during those hours. Hypoglycemia, in itself, like oxygen deprivation, is enough to cause convulsions.

Progesterone and thyroid promote normal energy production, and their deficiency causes a tendency toward hypoglycemia, edema and instability of nerves.

Twenty years ago, a woman who was considered demented visited me. From the age of 21, she had been increasingly disabled by premenstrual migraines. When she was 35 she was a school teacher, and during the summer a neurologist told her that dilantin would help her headaches, because "migraine is similar to epilepsy." Although she told the neurologist that the drug made her "too stupid to teach school," he offered her no alternatives, and didn't mention that sudden withdrawal from the drug could trigger a seizure. When classes started she discontinued the dilantin and had a seizure. The neurologist said the seizure proved that migraines were a form of epilepsy. At the age of 52, she spent about 20 h a day in bed, and couldn't go outside by herself, because she would get lost. After using a little progesterone for a few days, she stopped having seizures, discontinued her drugs, and was able to work. When she returned to graduate school, she got straight As, and earned her masters' degree in gerontology. But she had lost 17 years because the drug industry had covered up the role of the hormones in epilepsy, migraine, and the perimenstrual syndrome.

The most popular anticonvulsant drugs are both neurotoxic and teratogenic, that is, they damage the patient's brain, and greatly increase the incidence of birth defects. The Nazis justified their horrible medical experiments as "science," but the effects of epilepsy medicine in the last half century have been similar in effect, grander in scale, and without any scientific justification.

Besides the specific promotional efforts of the drug industry and their branch of government, there is a broader situation that makes their work easier. It is a culture of goony ideas, that ultimately emanates from the academic elite, which (since Descartes, and before) places "thought" above evidence. In biology, "genes" and "membranes" are confused ideas that are used to justify actions that aren't based on evidence. For the Nazis, "cultural degeneracy" was a medical-biological-political category based on that style of thinking. In the United States, "genes" for epilepsy, hyperactivity, language development, IQ, eclampsia, etc., are "found" at Harvard/MIT/Stanford/Yale/Univ. of California, etc., by an elite whose

wits have been dulled by environmental deprivation, that is, by a lack of criticism.

By manipulating the diet and environment, animals can be made more or less seizure-prone, and it happens that the changes that affect the brain affect all other organs, in ways that are now fairly well understood. Examining the cellular events associated with a seizure is useful for therapy and prevention of seizures, but the same methods are helpful for many other conditions. It is now clearly established that stress can cause brain damage, as well as other diseases. Now that our public health establishment has eliminated smoking from public places, maybe they can find a way to reduce stress and disease by removing morons from positions of power.

Excitotoxicity, in its simplest sense, is the harmful cellular effect (death or injury) caused by an excitatory transmitter such as glutamate or aspartate acting on a cell whose energetic reserves aren't adequate to sustain the level of activity provoked by the transmitter. Once an excitotoxic state exists, the consequences of cell exhaustion can increase the likelihood that the condition will spread to other cells, since any excitation can trigger a complex of other excitatory processes. As calcium enters cells, potassium leaves, and enzymes are activated, producing free fatty acids (linoleic and arachidonic, for example) and prostaglandins, which activate other processes, including lipid peroxidation and free radical production. Protein kinase C (promoted by unsaturated fats and estrogen) facilitates the release of excitatory amino acids.[3] Estrogen supports acetylcholine release, which leads to increased extracellular potassium and excitatory amino acids.[4]

Estrogen also stimulates the production of free radicals. Calcium, free radicals, and unsaturated free fatty acids impair energy production, decreasing the ability to regulate potassium and calcium. The increased estrogen associated with seizures is associated with reduced serum calcium.[5] Feedback self-stimulation of free radicals, free fatty acids, and prostaglandins create a bias toward increased excitation.

Ammonia is produced by stimulated nerves, and normally its elimination helps to eliminate and control the excitotoxic amino acids, glutamate and aspartate. The production of urea consumes aspartic acid, converting it to fumaric acid, but this requires carbon dioxide, produced by normal mitochondrial function. A deficiency of carbon dioxide would reduce the delivery of oxygen to the brain by constricting blood vessels

and changing hemoglobin's affinity for oxygen (limiting carbon dioxide production), and the failure to consume aspartate (in urea synthesis) and glutamate (as alpha-ketoglutarate) and aspartate (as oxaloacetate) in the Krebs cycle, means that as energy becomes deficient, excitation tends to be promoted. This helps to explain the fact that seizures can be induced by hypoxia. (Balloonists and mountain climbers at extremely high elevations have mentioned suffering from severe insomnia. The mechanisms of excitotoxicity are probably involved in other forms of insomnia, too.) Antioxidants help to control seizures, by reducing the excitatory contribution of free radicals and lipid peroxidation. Since excitation can promote the toxic forms of oxidation, many surprising substances turn out to have an "antioxidant" function. Magnesium, sodium (balancing calcium and potassium), thyroid and progesterone (increasing energy production), and in some situations, carbon dioxide. Aspirin, by inhibiting prostaglandin synthesis (and maybe other mechanisms) often lowers free radical production. Adenosine seems to have a variety of antioxidant functions, and one mechanism seems to be its function as an antiexcitatory transmitter. One of estrogen's excitant actions on the brain probably involves its antagonism to adenosine.[6]

Albumin, besides maintaining blood volume and preventing edema, serves to protect respiration, by binding free fatty acids. Estrogen blocks the liver's ability to produce albumin, and increases the level of circulating free fatty acids. Free fatty acids cause brain edema. This is probably another aspect of estrogen's contribution to seizure susceptibility. Magnesium sulfate has been used for generations in India to treat eclampsia and "toxemia" of pregnancy, and its effectiveness is gradually coming to be recognized in the U.S. Increasingly, magnesium deficiency is recognized as a factor that increases susceptibility to seizures.[7,8] Hypothyroidism reduces the ability of cells to retain magnesium. Thyroid does many things to protect against seizures. It keeps estrogen and adrenal hormones low, and increases production of progesterone and pregnenolone. It facilitates retention of magnesium and of sodium, and prevents edema in a variety of ways.

Progesterone, because of its normal anesthetic function (which prevents the pain of childbirth when its level is adequate), directly quiets nerves, and in this way suppresses many of the excitotoxic processes. It has direct effects on mitochondria, promoting energy production, and it facilitates thyroid hormone functions in various ways. It promotes

the elimination of estrogen from tissues, and is a "diuretic" in several benign ways, that are compatible with maintenance of blood volume. It antagonizes the mineralocorticoids and the glucocorticoids, both of which promote seizures.[9] The combination of hypoglycemia with elevation of cortisone probably accounts for the nocturnal incidence of seizures.

If progesterone's antiepileptic effectiveness were not enough (and it is very effective even in irrational pharmaceutical formulations), the fact that it reduces birth defects, and promotes brain development and nerve repair should assure its general use in women with a history of seizures, until it is established that they are no longer "epileptic." Although thyroid, progesterone, and a high quality protein diet will generally correct the epilepsy problem, it is important to mention that the involvement of unsaturated fats and free radicals in seizure physiology implies that we should minimize our consumption of the unsaturated fats. Even years after eliminating them from the diet, their release from tissue storage can prolong the problem, and during that time the use of vitamin E is likely to reduce the intensity and frequency of seizures. Coconut oil lowers the requirement for vitamin E, and reduces the toxicity of the unsaturated fats,[10] favoring effective respiration and improving thyroid and progesterone production. Endotoxin formed in the bowel can block respiration and cause hormone imbalances contributing to instability of the nerves, so it is helpful to optimize bowel flora, for example with a carrot salad; a dressing of vinegar, coconut oil and olive oil, carried into the intestine by the carrot fiber, suppresses bacterial growth while stimulating healing of the wall of the intestine. The carrot salad improves

the ratio of progesterone to estrogen and cortisol, and so is as appropriate for epilepsy as for premenstrual syndrome, insomnia, or arthritis.

> When the brain loses its oxygen supply, consciousness is lost immediately, before there is much decrease in the ATP concentration. This has led to the proposal of interesting "electronic" ideas of consciousness, but there is another way of viewing this. While ATP constitutes a kind of reservoir of cellular energy, the flow of carbon dioxide through the brain cell is almost the mirror image of the flow of oxygen. Oxygen scarcity leads directly to carbon dioxide scarcity. The "sensitive state," consciousness, might require the presence of carbon dioxide as well as ATP, to sustain a cooperative, semi-stable, state of the cytoplasmic proteins. The ability of ordinary light to trigger a conformation change in the hemoglobin-carbon monoxide-carbon dioxide system shows how sensitive a system with only a few elements can be. At the other extreme from consciousness, there is the evidence that carbon dioxide is essential for even the growing/living state of protozoa, algae, and bacteria.[11]
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> "The statement of Valley and Rettger that all bacteria need carbon dioxide for growth had been shown to apply to young as well as old cells." "…it is possible…to remove it as rapidly as it is produced, and under these circumstances, bacteria cannot multiply."[11, p. 113]

Estriol, DES, DDT, etc.

Ray Peat's Newsletter, 2010

POLLUTION of the environment and food supply by estrogenic chemicals is getting increased attention. Early in the study of estrogens, it was noticed that soot, containing polycyclic aromatic hydrocarbons, was both estrogenic and carcinogenic. Since then, it has been found that phenolics and chlorinated hydrocarbons are significantly estrogenic, and that many estrogenic herbicides, pesticides, and industrial by-products persist in the environment, causing infertility, deformed reproductive organs, tumors, and other biological defects, including immunodeficiency. In the Columbia River, a recent study found that about 25 % of the otters and muskrats were anatomically deformed.

Estrogenic pollution kills birds, panthers, alligators, old men, young women, fish, seals, babies, and ecosystems. Some of these chemicals are sprayed on forests by the U.S. Department of Agriculture, where they enter lakes, underwater aquifers, rivers, and oceans. Private businesses spray them on farms and orchards, or put them into the air as smoke or vapors, or dump them directly into rivers. Homeowners put them on their lawns and gardens.

Natural estrogens, from human urine, enter the rivers from sewage. Many tons of synthetic and pharmaceutical estrogens, administered to menopausal women in quantities much larger than their bodies ever produced metabolically, are being added to the rivers.

In the same way that weak estrogens in the environment may become hundreds of times more estrogenic by synergistic interactions,[2] combinations of natural, medical, dietary, and environmental estrogens are almost certain to have unexpected results. The concept of a "protective estrogen" is very similar to the idea of "protective mutagens" or "protective carcinogens," though in the case of estrogens, their promoters don't even know what the normal, natural functions of estrogen are.

In November, 1995, an international conference was held to study the problem of "environmental endocrine-disrupting chemicals," and to

A review of the use of estrogens reported in *JAMA* (only up to 1987) found nearly 200 different "indications" for its use.[1] Using the conservative language of that journal, such use could be said to constitute wildly irresponsible "empirical" medical practice. More appropriate language could be used.

devise strategies for increasing public awareness of the seriousness of the problem. Their "statement from the work session" says "new evidence is especially worrisome because it underscores the exquisite sensitivity of the developing nervous system to chemical perturbations that result in functional abnormalities." "This work session was convened because of the growing concern that failure to confront the problem could have major economic and societal implications." "We are certain of the following: Endocrine-disrupting chemicals can undermine neurological and behavioral development and subsequent potential of individuals…" "Because the endocrine system is sensitive to perturbation, it is a likely target for disturbance." "Man-made endocrine-disrupting chemicals range across all continents and oceans. They are found in native populations from the Arctic to the tropics, and, because of their persistence in the body, can be passed from generation to generation." "…many endocrine-disrupting contaminants, even if less potent than the natural products, are present in living tissue at concentrations millions of times higher than the natural hormones." "The developing brain exhibits specific and often narrow windows during which exposure to endocrine disruptors can produce permanent changes in its structure and function."

In spite of this increased exposure to estrogens, there is a new wave of advertising of estrogenic substances, based on the idea that weak estrogens will provide protection against strong estrogens. The environmental background of estrogenic pollution already provides a continuous estrogenic exposure. In the 1940s, Alexander Lipshuts demonstrated that a continuous, weak estrogenic stimulus was immensely effective in producing, first fibromas, then cancer, in one organ after another, and the effect was not limited to the reproductive system. How is it possible that the idea of "protection" from a weak estrogen seems convincing to so many? Isn't this the same process that we saw when the nuclear industry promoted Luckey's doctrine of "radiation hormesis," literally the claim that "a little radiation is positively good for us"?

DES (diethyl stilbestrol) is one of the most notorious estrogens, because studies in humans revealed that its use during pregnancy not only caused cancer, miscarriages, blood clots, etc., in the women who used it, but also caused cancer, infertility, and deformities in their children, and even in their grandchildren. (But those transgenerational effects are not unique to it.)

Besides the absurd use of DES to prevent miscarriages, around 1950 it was also used to treat vulvovaginitis in little girls, for menstrual irregularity at puberty, to treat sterility, dysfunctional bleeding, endometriosis, amenorrhea, oligomenorrhea, dysmenorrhea, migraine headaches, nausea and vomiting, and painful breast engorgement or severe bleeding after childbirth.

DES is a "weak" estrogen, in the sense that it doesn't compete with natural estrogens for the "estrogen receptors." (Estriol binds more strongly to receptors than DES does.[3]) Pills formerly contained from 5 mg to 250 mg. of DES.

The 1984 PDR lists doses for hypogonadism and ovarian failure as 0.2 mg/day to 0.5 mg/day. In general, dosage of estrogens decreased by a factor of 100 after the 1960s.

An aggressively stupid editorial by Alvin H. Follingstad,[4] is being circulated to promote the use of estriol, or the phytoestrogens. It argues that women who secrete larger amounts of estriol are resistant to cancer. By some tests, estriol is a "weak estrogen," by others it is a powerful estrogen.

When estriol was placed in the uterus of a rabbit, only 1.25 μg was sufficient to prevent implantation and destroy the blastocyst.[5] Since the effect was local, the body weight of the animal doesn't make much difference, when thinking about the probable effect of a similar local contentration of the hormone on human tissues. The anti-progestational activity of estriol and estradiol are approximately the same.[6]

When 5 mg. of estriol was given to women intravaginally, this very large dose suppressed LH within 2 h, and suppressed FSH in 5 h. Given orally, 8 mg. had similar effects on LH and FSH after 30 days, and also had an estrogenic effect on the vaginal epithelium. These quick systemic effects of a "weak estrogen" are essentially those of a strong estrogen, except for the size of the dose.[7]

When administered subcutaneously, estriol induced abortions and stillbirths.[8]

Another indication of the strength of an estrogen is its ability to cause the uterus to enlarge. Estriol is slightly weaker, in terms of milligrams required to cause a certain rate of uterine enlargement, than estradiol.[9] But isn't the important question whether or not the weak estrogen imitates all of the effects of estradiol, including carcinogenesis

and blood clotting, in addition to any special harmful effects it might have?

When added to long-term culture of human breast cancer cells, estriol stimulated their growth, and overcame the antiestrogenic effects of tamoxifen, even at concentrations hundreds of times lower than that of tamoxifen. "The data do not support an antiestrogenic role for estriol in human breast cancer."[10]

Studies of the urinary output of estriol/estradiol in women with or without breast cancer do not reliably show the claimed association between low estriol/estradiol and cancer, and the stimulating effect of estriol on the growth of cancer cells suggests that any alteration of the estrogen ratio is likely to be a consequence of the disease, rather than a cause. The conversion of estradiol to other estrogens occurs mainly in the liver, in the non-pregnant woman, as does the further metabolism of the estrogens into glucuronides and sulfates. The hormonal conditions leading to and associated with breast cancer all affect the liver and its metabolic systems. The hydroxylating enzymes are also affected by toxins. Hypothyroidism (low T_3), low progesterone, pregnenolone, DHEA, etiocholanolone, and high prolactin, growth hormone, and cortisol are associated with the chronic high estrogen and breast cancer physiologies, and modify the liver's regulatory ability.

The decreased output of hormones when the fetal-placental system is dying is a natural consequence, since the placenta produces hormones, and during pregnancy converts estradiol to estriol. Since estradiol in excess kills the fetus, its conversion by the placenta to estriol is in accord with the evidence showing that estriol is the more quickly excreted form.[11] The conversion of 16-hydroxy androstenedione and 16-hydroxy-DHEA into estriol by the placenta[12] would also cause fetal exhaustion or death to result in lower estriol production. But a recent observation that a surge of estriol production precedes the onset of labor, and that its premature occurrence can identify women at risk of premature delivery[13] suggests that the estriol surge might reflect the mother's increased production of adrenal androgens during stress. (This would be analogous to the situation in the polycystic ovary syndrome, in which excessive estradiol drives the adrenals to produce androgens.)

Estetrol, which has one more hydroxyl group than estriol, is a "more sensitive and reliable indicator of fetal morbidity than estriol during toxemic pregnancies," because it starts to decrease earlier, or decreases

more, than estriol.[14] This seems to make it even clearer that the decline of estriol is a consequence, not a cause, of fetal sickness or death.

A 1994 publication[15] reported that there are four hormonal features in women with breast cancer: diminished androgen production, luteal inadequacy, increased 16-hydroxylation of estradiol, and increased prolactin. The 16-hydroxylation converts estradiol into estriol.

A new technique for radiographically locating a hormone-dependent breast cancer is based on the fact that estriol-sulfate is a major metabolite of estradiol. The technique showed the tumor to have about a six times higher concentration of estriol-sulfate than liver or muscle.[16]

Another association of elevated conversion of estradiol to estriol with disease was found to occur in men who had a myocardial infarction, compared to controls who hadn't.[17]

The estrogens in clover have been known for several decades to have a contraceptive action in sheep, and other phytoestrogens are known to cause deformities in the genitals, feminization of men, and anatomical changes in the brain as well as functional masculinization of the female brain.[18–21] The effects of the phytoestrogens are very complex, because they modify the sensitivity of cells to natural estrogens, and also modify the metabolism of estrogens, with the result that the effects on a given tissue can be either pro-estrogenic and anti-estrogenic. For example, the flavonoids, naringenin, quercetin and kaempherol (kaempherol is an antioxidant, a phytoestrogen, and a mutagen) modify the metabolism of estradiol, causing increased bioavailability of both estrone and estradiol.[22]

Why do plants make phytoestrogens? There is some information indicating that these compounds evolved to regulate the plants' interactions with other organisms—to attract bacteria, or to repel insects, for example, rather than just as pigment-forming materials.[23] The fact that some of them bind to our "estrogen receptors" is probably misleading, because of their many other effects, including inhibiting enzyme functions involved in the regulation of steroids and prostaglandins. Their biochemistry in animals is much more complicated than that of natural estrogens, which is itself so complicated that we can only guess what the consequences might be when we change the concentration and the ratio of substances in that complex system.[8, p. 6]

These "natural" effects in sheep were forerunners of the observed estrogenic effects in wild animals, caused by pollutants. Twenty-five

years ago I reviewed many of the issues of estrogen's toxicity, and the ubiquity of estrogenic substances, and since then have regularly spoken about it, but I haven't concentrated much attention on the phytoestrogens, because we can usually just choose foods that are relatively free of them. They are so often associated with other food toxins—antithyroid factors, inhibitors of digestive enzymes, immunosuppressants, etc.—that the avoidance of certain foods is desirable. Recently an advocate of soybeans said "if they inhibit the thyroid, why isn't there an epidemic of hypothyroidism in Asia?" I happened to hear this right after seeing newspaper articles about China's problem with 100,000,000 cretins; yes, Asia has endemic hypothyroidism, and beans are widely associated with hypothyroidism.

When I first heard about clover-induced miscarriages in sheep, I began reading about the subject, because it was relevant to the work I was doing at that time on reproductive aging. Sheep which are adapted to living at high altitude, where all animals have reduced fertility, have an adaptive type of hemoglobin, with a greater affinity for oxygen. Fetal hemoglobin, in animals at sea-level, has a great affinity for oxygen, making it possible for the fetus to get enough oxygen, despite its insulation from the mother's direct blood supply. The high-altitude-tolerant sheep have hemoglobin which is able to deliver sufficient oxygen to the uterus to meet the needs of the embryo/fetus, even during relative oxygen-deprivation. These sheep are able to sustain pregnancy while grazing on clover. It seemed evident that estrogen and high altitude had something in common, namely, oxygen deprivation, and it also seemed evident that these sheep provided the explanation for estrogen's abortifacient effects.

Estrogen's effects, ranging from shock to cancer, all seem to relate to an interference with the use of oxygen. Different estrogens have different affinities for various tissues, and a given substance is likely to have effects other than estrogenicity, and the presence of other substances will modify the way a tissue responds, but the stressful shift away from oxidative production of energy is the factor that all estrogens have in common. Otherwise, how could suffocation and x-irradiation have estrogenic effects?

Pharmaceutical misrepresentations regarding the estrogens rank, in terms of human consequences, with the radiation damage from fall-out from bomb tests and reactor-leaks, with industrial pollution, with degradation of the food supply—with genocide, in fact.

Advertising gets a bad name when it can't be distinguished from mass murder. At a certain point, we can't afford to waste our time making subtle distinctions between ignorance and malevolence. If we begin pointing out the lethal consequences of "stupid" or quasi-stupid commercial/governmental policies, the offenders will have the burden of proving that their actions are the result of irresponsible ignorance, rather than criminal duplicity. From the tobacco senators to the chemical/pharmaceutical/food/energy industries and their agents in the governmental agencies, those who do great harm must be held responsible.

The idea of corporate welfare, in which public funds are given in massive subsidies to rich corporations, is now generally recognized. Next, we have to increase our consciousness of corporate responsibility, and that ordinary criminal law, especially RICO, can be directly applied to corporations. It remains to be seen whether a government can be made to stop giving public funds to corporations, and instead, to begin enforcing the law against them—and against those in the agencies who participated in their crimes.

In the U.S., the death penalty is sometimes reserved for "aggravated homicide." If those who kill hundreds of thousands for the sake of billions of dollars in profits are not committing aggravated homicide, then it must be that no law written in the English language can be objectively interpreted, and the legal system is an Alice in Wonderland convenience for the corporate state.

Estrogen, Memory and Heredity

Imprinting and the Stress Response

Ray Peat's Newsletter, 2009

RECENT work in several areas of biology is showing that heredity is not rigidly deterministic, in the way implied by traditional genetics, and it is opening the way for the development of therapies for incurable, chronic, or congenital problems, in natural and holistic ways that don't involve the mechanistic interventions of "gene therapy" or "genetic engineering." For example, nontoxic treatments for cancer that were demonstrated decades ago, were discarded because they didn't seem consistent with "genetics." Many problems that are classified as congenital or genetic, turn out to be physiological, and correctable. Even the brain and the heart, which until recently were considered to be incapable of regenerative repair, are now seen to be capable of great anatomical flexibility.

There are still great authoritarian forces opposed to recognizing, and supporting, the organism's full potential. The most useful therapies will remain in obscurity until many people see that those therapies have a firmer scientific foundation than orthodox (antiquated) medical genetics has. Over 100 years ago, Samuel Butler had an argument with Charles Darwin, and concluded that Darwin was philosophically muddled, and dishonest. Butler was annoyed that Darwin had belittled the work of his predecessors, including his grandfather, Erasmus Darwin. Butler was defending the idea of biological intelligence, the incorporation of experience into physiology and heredity.

My parents had an old copy of one of Darwin's books, and I was impressed by the fact that in his introduction, Darwin was careful to point out that his ideas were already being misrepresented, and that he did not hold "natural selection" to be the only mechanism of evolution, but that several factors were important, including sexual selection and the inheritance of acquired traits. I suppose those remarks might have been motivated partly by knowing that Butler didn't approve of the way he was behaving, but they didn't seem to have much influence on the way history has characterized Darwin's work. All of my biology professors would have been happier if Darwin had never made those remarks. I suspect that Darwin's problem was that any theory of evolution was under such

heavy attack that he couldn't devote much time to the relatively minor issue of how evolution works.

After Darwin's death, the study of heredity made some strange concessions to the culture of anti-evolutionism. As people began thinking about "particles that carry heredity," the "genes," ideas from the anti-evolutionist culture formed much of the context for understanding these "particles."

Darwin had suggested that the mature organism reconstitutes itself in the germ cells, by sending gemmules or pangens (buds or sprouts or derivatives) from its various parts, so that the parent's traits would be incorporated into the reproductive cells. This was called pangenesis, meaning that the whole organism was the source for the new offspring. This theory opened the possibility for newly acquired traits to be passed on. It grew out of the experience of animal breeders and horticulturists, who were dedicated to improving their breeds and strains, by selecting the best individuals grown under the best conditions. It was known that the miniature ponies, Shetlands for example, would grow larger each generation when bred under favorable conditions of domestication, rather than under the harsh conditions of their native island. It apparently never occurred to most plant and animal breeders that they might be able to improve a breed by subjecting it to harmful conditions.

Around the end of the 19th century, August Weismann began a systematic attack on the ideas of Darwin. As part of his campaign, he invented the doctrine that the reproductive cells are absolutely isolated from the rest of the organism, and that they are immortal. The rest of the organism is built up by the deletion of genetic information. This doctrine was very convenient for those who maintained that all organisms had been created in a single moment, and that the appearance of evolution resulted from the extinction of some species, but not the new appearance of some species. Some people, reasoning from Weismannism, suggested that evolution might have resulted without any change in the immortal genetic material, except deletion, in a manner analogous to Weismann's theory of the developing individual. Bacteria, in that view, would contain all the genes needed to make a tree or a person, and the more complex forms would have evolved through the differential loss of that primeval genetic information.

The changes produced by subtraction were compatible with the notion of fallen man in a corrupt world, while the addition of heritable

traits through experience would connote a sharing in the process of creation. The hereditary particles making up Weismann's "immortal isolated germ line" connoted a single original creation.

As mutations in the genes came to be seen as a reality, experiments with X-rays suggested to some that all mutations were harmful, and this attitude blended into the stream of doctrine which insisted that no improvement could be inherited. Although many experiments showed what seemed to be meaningfully directed mutations, the doctrine held its ground, as its advocates taught that mutations were always random. (The doctrine of random change, like the idea that entropy only increases, excluded acts of creation from the fallen material world.) If a new trait appeared under new conditions, it was said to be only because an old trait was being revealed by the induced loss of another trait.

I think anyone who reads the "landmark publications" in genetics will see that genetics had very little to do with scientific method, as commonly conceived, and that it had all the traits of a cult. Analysis of the language of genetics reveals that terms have more often been used to cover up empty speculation than to clarify situations of fact.

Parallel to the way Darwin infuriated Samuel Butler by misrepresenting the origins of his theory, the neodarwinists who debate the creationists over school textbooks are ignoring the ways in which the culture of antievolutionism shaped their own view of genetics.

The discovery of enzymes that produce DNA modeled on RNA, "reverse transcriptases," began undermining traditional genetics, because it showed that new information can enter our genome.

The discovery that bacteria can pass "genes" from one individual to another, conferring antibiotic resistance upon previously sensitive strains, was a major nuisance to people working in infectious disease, since it complicates the treating of disease, but it indicated that "evolution," or genetic change, was capable of happening in non-random ways.

Early in the study of viral genetics, many people realized that "organisms" which can't reproduce without their relatively complex hosts, presented a problem for evolutionary theory. If the virus requires a cell in order to exist, it is hardly a separate organism. A few people suggested that viruses were, or were based on, functional normal parts of higher organisms. Some researchers have suggested that virus-like particles serve to carry information from one part of an organism to other parts

of that organism. Mobile genetic elements are now well recognized, operating within cells, and it is common laboratory practice to use viral particles to transfer genetic material from one cell to another.

Cellular systems which cut and splice nucleic acids, creating sequences of information which don't exist in the inherited chromosomes, are now accepted parts of cell biology. Hormonal and environmental influences on the stability of messenger RNA, and on mobile genetic elements, and on genomic stability in general, are recognized. The center of gravity in the study of the nucleic acids has now shifted from heredity to development. Almost nothing remains of Weismannism, which was the foundation of neodarwinism. The "isolation of the germline" doctrine persists in a few places, such as explaining why "the ovary runs out of eggs," despite some examples of egg-cell renewal.

But when the identity of "germline cells" is found to depend on signals from the environment, the last vestige of Weismannian germline doctrine disappears. The only meaning of "germline" is that some cells are destined to be germ cells, and the meaning disappears when such cells differentiate to form body parts.[1,2]

The difference between primordial germ cells and embryonic cells is a matter of "imprinting," the process in which a hormone or "growth factor" or other "signal" directs a cell down a certain course of differentiation. "Imprinting" is where genetics and physiology, phylogeny and ontoneny, come together, and the new facts that are being discovered are removing the last vestige of scientific content from Weismannism/neodarwinism.

The argument between Peter Duesberg and the virus establishment, in which Duesberg argues that acquired immunodeficiency is produced by a variety of causes, including drug use, and the establishment argues that the HIV retrovirus is the only cause, becomes a little clearer when we consider it in the context of the larger debate between the genetic determinists and the Darwinian adaptationists. I will talk about that in more detail in a newsletter on immunodeficiency.

The issues of cancer, aging, and "hormone receptors," are also illuminated by seeing the organism as capable of adaptive modification of its genes.

These newer molecular approaches to the study of biology are vindicating some of the practical observations of plant and animal breeders, and terms such as telegony, heterosis, and xenia might come into com-

mon use again, along with genomic imprinting. Here, I want to give examples of "hormonal imprinting" and "genetic imprinting," and to show how the idea of the "retrovirus" or "mobile genetic elements" relates to practical health issues and therapies. The developing egg cell is constructed and modified in many ways during its growth. The nurse cells which surround it in the ovarian follicle inject massive quantities of material, especially RNA, into the expanding egg cell. Regulatory substances and energy production modify enzyme activities and structural proteins, which will influence the way it develops after fertilization. During the entire lifetime of the individual person, the developing egg cells are open to influences from the organism as a whole. Because of the Weismannian scientific culture, it's important to start with a few of the clearest interaction between the environment and the reproductive cell, but many other types of interaction are starting to be explored.

It has been suggested that environmental stress is responsible for viral epidemics, by activating viruses in their animal hosts, and causing them to spread to humans. Whether that's true or not, it is well recognized that stress causes increased susceptibility to the development of viral infections. It also causes increased genetic variability, which is logical in the evolutionary sense, that a species should become more variable when its environmental niche has changed. The mobile genetic elements that were first recognized by Barbara McClintock are now considered to be the most important means by which stress increases genetic variability.

In bacteria,[3,4] genetic changes are known to occur in response to specific substances, which lead to adaptation to that substance. The mobile elements which are responsible for the defensive adaptive response to antibiotics are similar to viruses. In these instances, the genetic dogma which has been taught very recently in the universities couldn't have been more clearly disproved. So far, the tendency in the United States is to concentrate on the details because of their technological potential (for genetic engineering of lucrative products) and to ignore the larger biological meaning of this interaction of stress with genetics.

Resistance to antibiotics is transmitted to other bacteria by "injecting," during conjugation of a resistant bacterium with a sensitive one, a small virus-like granule containing the DNA required for detoxifying the antibiotic, along with some adjoining genes. The antibiotic itself, producing stress, stimulates the formation of this genetic package.

(Whole university courses used to be devoted to showing why such things couldn't happen.)

The enzymes which cut out sections of DNA are the "restrictases," which are famous for their use in identifying samples of DNA. These "endonucleases" are activated by stress. In "excitotoxicity," which kills nerve cells through a combination of intense activation with deficient energy stores (i.e., stress), these enzymes are activated.

In apoptosis, or "programmed cell death," these enzymes are activated, along with enzymes which repair the broken genes, and the resulting energy drain from an impossible repair job causes the cell's sudden dissolution. Between excitotoxicity and apoptosis, there are intermediate states, in which the dissolution is retarded or reversed.

When the stress is more generalized, so that the cells survive, the more sensitive sections of DNA are rearranged within the cell. Some of them may escape as infective particles.

Barbara McClintock wrote about the effects of stress causing genetic rearrangement, and traced the movements of the mobile genetic elements. At the same time, without knowing about her work, Leonell Strong was working with mice, exploring the role of "genetic instability" in causing cancer, and identifying estrogen and "milk particle," or "milk factor," a virus-like particle that interacted with estrogen, as causes of breast cancer.

With only the elements of stress, the endonucleases, and the mobile packets of genes, adaptively increased variability, and the spreading of genes among a population can be explained. However, there is a subtler level at which the adaptations acquired by an indiviual can be passed on to offspring. This is "imprinting."

"Genetic imprinting" is being studied mainly in terms of the covering of regions of DNA with methyl groups. This is thought to have evolved as a way to keep the endonucleases from attacking the DNA. Sections of DNA that have been methylated can be passed on to offspring in that form, and they can be traced as a pattern of gene activity or inactivity. The maternal genes function in a manner identifiably different from the paternal genes. Having passed through the mother's body, the genes have been modified.

"Hormonal imprinting" refers to the great changes in sensitivity to hormones (and related substances) that persist after exposure to that substance early in life. When the mother's hormones are imbalanced

during pregnancy or nursing, the baby is "imprinted" with an altered sensitivity to hormones. Leonell Strong showed that these effects could be exaggerated generation after generation. But—strangely, considering that he was a student of T. H. Morgan, who is considered to be the founder of classical genetics—Strong found that a single treatment, or a series of treatments, with an extract of liver, or with certain nucleosides (the units for constructing DNA), could reverse the course of generations of breeding, and eliminate the susceptibility to cancer.

In modern terms, he was probably working with a combination of genetic imprinting and hormonal imprinting. His "milk factor" very probably was one of the "endogenous retroviruses," or mobile genetic elements.[5]

Movable genetic elements appear to regulate normal developmental processes[6] and the introduction of new particles can "improve fitness." This is an aspect of the HIV controversy that has been completely ignored, as far as I can tell. Peter Duesberg argues that the presence of antibodies to the HIV indicates that the immune system is active, and that there is no evidence showing the virus to be harmful. My suggestion would be that the virus is probably present quietly in many people who have no antibodies to it, and that environmental toxins and other stressors cause it to be adaptively expressed, creating the possibility for an antibody response. The "viral particle" itself might be biologically useful, though this wouldn't exclude the possibility that an abnormal immunological response to it could have harmful repercussions.

The importance of the retroviruses in the human genome hasn't been widely appreciated. ("almost 10%...homology with the retroviruses."[7])

Environmental pollution with estrogens and immunosuppressive substances, when it persists throughout the developmental period, and across generations, will be dangerous at levels much below those that show an immediate hormonal or immunosuppressive effect. Tests that determine the "mutagenicity" or "carcinogenicity" of a substance are performed within a context of a theoretical genetics which is demonstrably false; until the complexities of imprinting and transgenerational effects are taken into account, it would be wrong to accept the claim that there are "safe levels," or "thresholds of harmful effects."

When babies are imprinted by the mother's diuretics, by milk substitutes, and by industrial effluents, the worst effects are likely to be seen decades later, or even generations later.

There is a simple image that I think makes it possible to grasp as a whole the unity of things which have been described as existing on different "levels," the genetic, the metabolic, and the ecological. This is the image of an interaction between water and large molecules, such as proteins and nucleic acids, with the system—the way the large molecule is folded, and the way the water molecules are ordered—having more than one arrangement, or physical state, each state differing slightly in the amount of potential energy it contains. Then, the differences between respiratory energy (producing carbon dioxide and consuming electron-equivalents), and relatively anaerobic conditions, determine the probability that the system will return to its higher energy state after it has been perturbed.

A brief perturbation amounts to simple perception and response, reflecting the basic "irritability" of life, to use Lamarck's term. But with more intense disturbances, the structures are altered at deeper levels, and structures will be restored with different degrees of completeness, and the organism will have adapted, according to its resources, either toward increased "fitness" and sensitivity, or toward decreased sensitivity.

On the level of an individual, the movement away from fitness and sensitivity would resemble the development of aging and degenerative disease; on the level of a species, it would amount to "reverse evolution," a mammal would become more reptilian, a primate would become more rodent-like.

Protective interventions, and therapies, will consist of things which protect the structures (preserving sensitivity, while blocking excessive stimulation), and which increase the energy resources. A great variety of physiological indicators show that substances such as progesterone, thyroid and carbon dioxide are acting "universally" as protectants, in ways that make sense only with some perspective such as this, of the systematic changes in the physical state of the living substance.

Estrogen, Progesterone, and Cancer

Conflicts of Interest in Regulation and Product Promotion

Ray Peat's Newsletter, 2007

ISSUES that at first seem scientific too often turn out to be merely propagandistic. When a claim has no scientific value, it's necessary to directly attack that claim, but the propagandist hopes to (and often does) control the discourse, by resorting to techniques such as censorship, public relations, and financial-political power. The pharmaceutical industry uses all of those anti-scientific powers just as effectively as the military-industrial lobby does.

While Donald Rumsfeld answered the question, "where are the weapons of mass destruction?" by saying "We know where they are. They're in the area around Tikrit and Baghdad and east, west, south and north somewhat," the estrogen industry responds to the evidence that estrogen causes breast cancer, strokes, heart attacks, blood clots and Alzheimer's disease by saying "it's progesterone that is responsible."

To deal with the antiscientific fraudulent claims of the estrogen industry, it isn't necessary to search every square meter of Iraq, as it was with Rumsfeld's claim; it's enough to show that there is no science involved in their claims, by analyzing their experimental methods. But it's also important to examine some of the methods they have used to further their goals, despite the absence of any factual basis.

For more than 60 years, the estrogen industry has been using the techniques of public relations, including the placement of pseudoscientific articles in medical journals, to promote their sales. Recently, Carla Rothenberg documented a conspiracy of the estrogen industry in the 1940s to get medical and governmental approval of their products by shifting attention away from the clear evidence of estrogen's toxicity. Her paper competently reviews the subsequent history of "hormone replacement therapy."

> "The term cancer refers to a new growth which will invade surrounding tissues, metastasize (spread to other organs) and may eventually lead to the patient's death if untreated.
>
> A tumor is not necessarily a cancer. The word tumor simply refers to a mass. For example, a collection of pus is by definition a tumor. A cancer is a particularly threatening type of tumor." — *What is Cancer?* (Johns Hopkins University)

After 2002 when the Women's Health Initiative study announced some of the harmful effects of hormone treatment, resulting in a disastrous decrease in estrogen sales, the industry has intensified and diversified its public relations efforts, and has succeeded in recovering some of their lost market. Historically, whenever some of the claimed benefits of estrogen have been disproved, the industry shifts its emphasis to new, previously unmentioned "virtues" of the product. Hundreds of different benefits claimed for estrogen in prestigious medical journals have been proven false, but until 2002, the industry's profits grew steadily. Now, compensating for the annual loss of billions of dollars, they are highly motivated.

Dozens of toxic effects of estrogen were demonstrated and never refuted, but a variety of techniques of distraction and misdirection gradually emerged, to prevent the accumulated evidence of estrogen's toxicity (and/or ineffectiveness) from interfering with the campaigns to market it for the widest possible variety of conditions.

Since the WHI study involved the use of Prempro (PREMPROTM-conjugated estrogens and medroxyprogesterone acetate), the emphasis of the industry has been to divert attention from the toxic effects of estrogen, by blaming everything on "progesterone." An intense campaign is underway to assign all of estrogen's harmful effects to progesterone.

The pharmaceutical industry has a long history of lying about natural progesterone (and many other natural substances), to promote sales of their competing products. The price ratio of retail estrogen tablets to bulk estrogen can be 1000 to 1, while the ratio for progesterone products is often less than 10 to 1. With the increased use of progesterone (its sales in the U.S. have increased more than 100-fold), the estrogen industry has had to develop new kinds of attack. A small shift of the market away from estrogen costs the drug industry hundreds of millions of dollars. The loss of estrogen sales following the 2002 WHI study, that convincingly demonstrated its toxicity, was huge, with the decreased sales of Wyeth alone amounting to billions of dollars. Wyeth has petitioned the FDA to prevent compounding pharmacies from selling the natural hormones.

People who have made a career of research that, according to them, reveals the "benefits" of estrogen have, in recent years, expanded their work to argue that it is progesterone, rather than estrogen, that causes diabetes, heart disease, dementia, and cancer.

The EPA currently has a document draft on the internet which, in relation to the evaluation of a carcinogenic herbicide, reviews the issue of the balance between estrogen and progesterone in the development of cancer in rats, and includes the observation that progesterone is not carcinogenic to rats, and that it instead is protective against cancer, because of its antiestrogenic effects.

Recently, stores in California have placed warnings near their progesterone-containing cosmetics, saying that the State of California "knows" progesterone to be a carcinogen.

Californians often talk about their state's having the world's sixth largest economy. The state accounts for 14 % of the GDP of the U.S. If the state regulates a product made in Michigan, Texas, or France, the producer is very likely to change the product to suit California.

If an industry wants to control its competitors or potential competitors, an investment in California's regulatory system can pay huge rewards.

California has listed progesterone as a carcinogen under the Safe Drinking Water and Toxic Enforcement Act, called Proposition 65. The law doesn't prevent the sale of carcinogens, it simply requires a warning. Warnings are posted in grocery stores and restaurants, on sports equipment, in beauty parlors, on apartments and parking lots, but there is so little effort spent on realistic evaluation of risks that the effect of the law is to allow the major polluters to go unnoticed among the ubiquitous warnings. But California has other laws that encourage its lawyers to sue for "unfair business practices" when they believe Prop 65 has been violated. That has resulted in a culture of vigilantism with bounty-hunting lawyers, some of whom try to enforce Prop 65 even against companies that are clearly exempt.

California's regulatory board that lists progesterone as a carcinogen cites two bodies that have evaluated carcinogens, the US National Toxicology Program (NTP), and the UN's International Agency for Research on Cancer (IARC), as authoritative sources. One of those, the US National Toxicology Program (NTP) cites the other's, the IARC's, evaluation of progesterone as the basis for its own listing of progesterone, so the opinion of IARC has been very influential.

The IARC publications discussed the toxicity of several of the synthetic progestins, and concluded that some of them are possible human carcinogens. The (1987) entry for medroxyprogesterone acetate, for

example, has three sections: "A. Evidence for carcinogenicity to humans (inadequate)," "B. Evidence for carcinogenicity to animals (sufficient)," and C., that it can damage chromosomes. Eight citations, besides two IARC monographs,[1,2] are given as supporting evidence.

The entry for progesterone, oddly, has only two sections, "A. Evidence for carcinogenicity to animals (sufficient)," and B, that it doesn't damage chromosomes. There is no mention of human carcinogenicity at all. Besides the IARC monographs, only one study is mentioned, a test in beagles (I'll comment on the competency of that study below). At the end of the whole section, which included eleven synthetics and progesterone, it concludes: "Overall evaluation" "Progestins are possibly carcinogenic to humans (Group 2B)," oddly neglecting to distinguish progesterone from the synthetics.

The corruption of the term "progestin" or "progestogen" by the industry and the drug regulators has been terribly consequential. The synthetic chemicals classified as progestins often have anti-progesterone actions, and shouldn't be called progestins at all, because they don't support gestation, contrary to what the term falsely implies. It is exactly their anti-progesterone/antigestational action that led to their use as contraceptives.

Since the 1987 review by IARC, it seems that their only other review of progesterone's carcinogenicity was of a single study in 1999, and that study clearly gave evidence that progesterone prevented cancer.

But California's board of "qualified experts" in the Office of Environmental Health Hazard Assessment (OEHHA) identify progesterone as known to cause cancer, and cites the group of studies listed by IARC in the medroxyprogesterone acetate report as their evidence. Rather than trying to clarify the confusions that exist in the IARC documents, this board has compounded the confusion.

In the transcript of the meeting, at which they decided to list progesterone as a carcinogen, they received testimony from only one outside expert, Richard Edgren, who answered the chairman's question, why don't you want progesterone listed, by saying, because it isn't a carcinogen. He said that the inclusion of a large number of non-carcinogenic materials "could vitiate the use of the list."

But the chairman had, early in Edgren's review of the shortcomings of animal studies of carcinogenesis, heard the word "metastasis," in connection with beagle dogs, and—although Edgren hadn't said

that any metastatic cancer had been found in the progesterone test (it hadn't)—the committee's decision to list progesterone appears to have hinged on that word.

Edgren, referring to "various synthetic and semi-synthetic progestogens," said that administering them by injection "leads to the development of mammary nodules, some of which have the characteristics of malignant tumors, although these tumors rarely metastasize." A little later, Kilgore said "I mean, I heard you say that it was rare that it metastasized. I would say any kind of metastasizing is important." Edgren isn't quoted in the transcript as having attempted to explain that the malignant and metastatic cancers appeared only in beagles treated with synthetic progestins. At best, the behavior of the chairman and the committee, as reflected in that transcript, was erratic and confused, or more accurately, irrational.

The only biologist on the committee who spoke during the meeting, Dr. Spangler, expressed confusion and dissatisfaction with the evidence:

"…in reviewing the information that was supplied to me regarding progesterone, I was confused and concerned by what appears to be a variety of discrepancies in the way the compound has been reviewed." "In one place, IARC says there is limited evidence; in another place, it says there is sufficient evidence. And NTP says there is sufficient evidence. And they cite as their sufficient evidence a variety of very convoluted experimental procedures, in which mouse mammary tumor virus positive mice were used in a study; and, in addition to that, some other carcinogen, some other potent carcinogen, was applied at the same time or after." "It was just very confusing. And I had a lot difficulty evaluating it."

The State's rules explicitly state that all the relevant evidence is to be presented to the committee for consideration, and that the evidence must show clearly, by accepted scientific methods, that a material causes cancer (i.e., malignant tumors) before it can be listed. What is clearly shown by the few papers provided to the committee is that their procedures were not followed at all. Providing publications that didn't even claim to have involved the development of cancer, and ignoring an immense amount of more relevant evidence, the committee, in a parody of legal process, didn't even get a randomly selected sampling of the relevant evidence.

In my correspondence with OEHHA, when I pressed for information regarding the criteria for selecting evidence, and the qualifications of the staff who had the responsibility of selecting "all relevant evidence," their response was that they lacked the resources to answer the question.

Edgren, who had argued that progesterone wasn't a carcinogen, didn't make a very good presentation of the case against the few studies that had been mentioned by NTP and IARC. Even if he had been able to do that, in the few minutes he had (six or seven different substances were on the agenda for consideration for listing during that meeting), it doesn't seem likely that the committee would have been interested.

In a letter he wrote to the committee before it met, Edgren said "Careful evaluation of data from a properly conducted oral study is a prerequisite before the carcinogenicity of any chemical can be adequately evaluated." The reason for that statement is that it had become clear in the 1970s and 1980s that the invasive introduction of anything into the body's tissues creates inflammation and a complex series of systemic stress reactions that affect the immune system, and that can lead to the development or promotion of cancer, no matter how inert and innocuous seeming the injected material might be. The people on the committee didn't even discuss that issue. Worse, the studies mentioned by IARC included some that hadn't met basic scientific standards of experimental design, failing to use proper experimental controls, including vehicle controls, and failing to describe the actual composition of the vehicle or solvent used for administering progesterone.

Every good high school science teacher or science student knows that the experimental variables have to be clearly defined. The United Nations' IARC, the U.S.'s NTP, and California's Panel of Qualified Experts chose to draw conclusions on some studies that don't meet any standards for testing carcinogens, such as those published by the U.S. government. And while disregarding basic standards of experimental design, their review of the literature had an even more serious flaw—it "cherry-picked" the published evidence that they apparently preferred, ignoring the studies which, over a period of more than 20 years, showed that progesterone prevents and/or cures tumors. And in an extremely unrepresentative selection of studies on the subject of progesterone's carcinogenicity, the selected studies presented some clear evidence of some of progesterone's anticarcinogenic effects, along with some results that can't be interpreted clearly.

One of the early papers listed as evidence of progesterone's carcinogenicity in animals actually concluded that their experiments completely failed "to produce any beneficial effect by the administration of progesterone on the mammary cancer in mice," and cautioned that their results showed "the need for care in attempting to generalize results even in different strains of the same species and emphasizes the difficulty of attempting to carry over results obtained in experimental animals to human pathology."[3]

The work (demonstrations of the anti-tumor effect of progesterone) that they were not able to confirm had included explicit observations that intermittent injections of progesterone were not effective in preventing tumors or causing them to regress, and emphasized the importance of continuous exposure. Knowing that, the Burrows and Hoch-Ligeti publication appears to have been designed propagandistically to oppose the work that was demonstrating the anti-tumor actions of progesterone, since they—without explanation—used the already discredited method of giving periodic injections of progesterone dissolved in peanut oil.

Without reading the article, people seeing it included on the agencies' list of studies supposedly providing evidence of progesterone's carcinogenicity would assume that it provided such evidence. It didn't. If the agencies cite this study, why didn't they mention any of the numerous studies showing that progesterone prevents tumors or causes them to regress? The reason this study was done was to argue against the studies that had demonstrated progesterone's protective effects, so anyone reading it had to know of those other studies' existence, as well as knowing that this study itself provided no evidence at all of carcinogenicity.

Reproducibility is the essence of science, and the anti-tumor effects of progesterone were repeatedly demonstrated by different investigators. The single study by Burrows and Hoch-Ligetti has never been replicated, and the reason for its failure to show an anti-tumor effect was already explained by the other workers.

Since the 1920s, many studies had demonstrated that "spontaneous" cancers increase in proportion to the quantity of polyunsaturated fat (especially linoleic acid) in the diet. By the end of the 1960s, the carcinogenicity of vegetable oils, or at least their "co-carcinogenicity" or "tumor promoting" effects had become widely known, and one of the World Health Organization publications observed that progesterone

carcinogenicity studies using vegetable oil as the vehicle couldn't be recognized as valid.

More recently, ethanol has been found to antagonize progesterone's anticancer and anti-proliferative actions.

Studies using implanted pellets or plastic tubes containing a solution of progesterone sometimes neglected to even mention the nature of the solvent used. Since implanted pieces of inert materials, such as disks of plastic, could be carcinogenic, it was recognized that a proper control for a hormone-containing pellet or tube would require the implantation of a pellet or tube without the hormone. Sometimes, instead of actually implanting the object, sham surgery, similar to that involved in implantation of the pellet, would be used, in recognition that the surgical trauma itself could have far-reaching effects on the organism.

Any tissue damage or irritation causes the release of cytokines and mediators of inflammation, which are known to be involved in tissue growth and cancer. When injected, even plain water and other normally harmless things are carcinogenic.

The need for proper experimental controls when using implanted devices is shown by a study that analyzed the fibrotic tumors that had grown around implanted plastic tubes. Crystals of talc were found in the tumor, that were assumed to have originated from the surgical gloves used during the operation. Talc is now widely recognized as a carcinogen, and is suspected of causing ovarian cancer.

Overlooked variables are the reason for the essentiality of repeatability and confirmation in science.

In the 1970s, a new method for suspending or dissolving oily chemicals in water was being explored. A cyclic carbohydrate, cyclodextrin, makes it possible to wet substances that are insoluble in water, such as progesterone, even if the substance remains in a solid crystalline form. Several companies were promoting the use of these for the administration of hydrophobic drugs.

In 1976, D.W. Frank reported that the cyclodextrins produced nephrosis in rats. In 1978, a study by Perrin, et al., reported its toxicity to the kidneys. Twenty years later, Horsky and Pitha at NIH reported that the cyclodextrins can synergize with carcinogens, and in 1982 a group in Japan reported that cyclodextrins can increase the production of kidney cancers by another carcinogen.[4] The intrinsic carcinogenicity of a more water soluble cyclodextrin, that was considered "more toxicologically

benign," was found to cause pathological changes in lungs, liver, and kidney, and to increase the formation of tumors in the pancreas and intestines of rats.[5]

In 1974, D. W. Frank and others at Upjohn had begun testing the effects of progesterone and medroxyprogesterone acetate in beagle dogs, using an "aqueous suspension." Their 1979 publication describing that four year study didn't mention the way in which the "aqueous solution" had been made, and didn't mention cyclodextrins at all. Frank's published observation during the beagle study that cyclodextrins are toxic to the kidneys suggests that someone at Upjohn had noticed a problem with the "wetting agent" that was already in use in the beagle study.

Another remarkable feature of the four year beagle study was that, of 140 dogs that began the intended 7 year study, 28 had died by the time they published the report, and none died of cancer, but the causes of death were not reported. The only experimental group in which there were no deaths by the end of four years was the low dose progesterone group. The dogs in the high dose progesterone group received weekly intramuscular injections of 1140 mg of progesterone suspended in 11.4 mL of "aqueous vehicle." 2345 mL of the vehicle was received by each dog during the four years. Only four dogs in that group were still alive at the time of publication, but the cause of death of the other 16 wasn't mentioned. Quarts of a toxic material that had never before been used in this way, injected into their muscles, and the unexplained deaths of so many animals, make this a unique experiment that is unlikely ever to be repeated.

Their failure to mention injection-site muscle damage is just another indication of the study's low quality.

At the time of the study, it had been known for many years that interference with the organism's detoxifying systems, especially the liver and kidneys, can contribute to the development of cancer. Although the study was planned to continue for 7 years to meet the FDA requirement, none of the eight authors ever published again on a related topic, and most of them didn't publish again at all.

When I tried to contact one of the authors, he didn't respond. I assume they were embarrassed by the shoddiness of their methods. Richard Edgren has commented, "I can't believe how fast and how completely they shut down. They fired people and retrained the rest for other areas."

But the regulatory agencies have tied their reputations to studies of that sort.

No malignant cancers were reported in this four-year beagle study. Beagles normally have a high incidence of cancer, especially mammary cancer. In a different study in which 172 beagles were treated with contraceptive hormones, nine of them developed malignant cancers, and of those, five metastasized. (This might be why the chairman of the committee was thinking about metastatic cancer, but if so, he was simply confused, because the issue they were considering was the listing of natural progesterone, which wasn't reported to have produced any malignant or metastatic tumors.)

Two other studies cited by the IARC and other agencies, by Jones and Bern,[6] and Rebout and Pageaut, hardly seem appropriate studies to support the idea that progesterone is carcinogenic.

Jones' and Bern's paper described the production, 12 months after neonatal treatment with progesterone, of vaginal and cervical lesions, and mammary nodules, which are also referred to as tumors. "Progesterone alone induced cervical lesions in only 1 of 32 mice…and induced vaginal lesions in only 2 or 32 mice. Furthermore, progesterone given with either dose of estrogen to intact mice reduced the incidence of hyperplastic lesions, compared with intact groups treated with estrogen alone." They commented (page 74) that their results were "mammary tumor virus dependent," and that this might account for the production of "hyperplastic alveolar nodules as opposed to" tumors of possible ductal origin, that had been seen in other studies when the carcinogen DMBA was used.

In another 1977 publication,[7] Jones, Bern, and Wong described changes seen when the mice were 1.5 to 2 years old. This later publication appears to clarify the meaning of nodules or tumors in the younger animals: "Although mammary tumors were observed neither in control nor in progesterone-treated intact mice, many of the latter group possessed hyperplastic alveolar-like mammary nodules and other dysplasias." Neither of these studies refers to the carcinogenicity of progesterone.

The 1977 study (at the University of California, Berkeley) was explicitly motivated by Jones' and Bern's concern with the risks of the medical practice of treating pregnant women with DES and a synthetic progestin, and they used mammary tumor virus-bearing mice, and they didn't

continue the study to observe the incidence of actual cancers. (Their choice of infant rodents to study progesterone might be questioned, because of earlier work showing that immature rat ovaries are able to convert progesterone to estrogens, unlike the tissues of other animals or humans.[8,9])

Anyone working with mammary tumor virus-bearing mice in the 1970s should have been aware of the effects of sex hormones on the expression of virus and development of cancer in the infected mice, as studied by Strong, Figge, and others for about 40 years. Excess estrogen causes the virus to be expressed, progesterone opposes its expression.

Jones and Bern injected the newborn mice with 0.02 mL of sesame oil daily for five days, with or without estrogen and progesterone. A newborn mouse weighs a little over a gram. On a weight and volume basis, this would be like injecting an adult human with more than a quart of sesame oil daily for five days. The proportionate weight of progesterone in an adult human would be several grams per day.

This amount of progesterone is far more than the anesthetic dose. Since the authors didn't mention anesthesia, very little of the progesterone could have been absorbed, meaning that deposits of crystals would have remained in their tissues.

Tissue irritation from foreign bodies and from vegetable oil, even in relatively small amounts, can produce severe systemic reactions, because of the reactive production of nitric oxide, prostanoids, and a great variety of pro-inflammatory and tumor-promoting cytokines.

This study might have had the formal appearance of a scientific experiment, but the unfamiliarity of the men with the material they were using, their use of mice carrying the mammary tumor virus, and, more importantly, the extremely complex reactions produced when extraneous materials are injected into the tissues, make this a useless experiment. The value of Richard Edgren's statement about the need to test carcinogens orally, rather than by injection, is becoming clearer all the time, as the role of irritation in cancer development is being better understood.

In their second 1977 study, Jones, Bern and Wong reported that at the age of 1.5 to 2 years, nearly two thirds of the progesterone treated mice had genital tract lesions. In another study published in 1977 (Iguchi and Takasugi) neonatal mice were given the same daily amount of progesterone, but for ten days rather than five, giving them twice the dose.

These authors reported that there were no permanent changes in the vaginal and uterine epithelium. This study wasn't mentioned by any of the agencies, but it calls the results of the California study into question.

In a 1973 study by Rebout and Pageaut, progesterone was administered in a pellet, the composition of which was not mentioned, and there was no vehicle control at all. Each mouse received 45 mg of progesterone. The average mouse weighs about 30 g. Invasive squamous carcinomas were produced by the carcinogen 20-methylcholanthrene, and these were more numerous in the progesterone treated mice. Methylcholanthrene is an extremely hydrophobic, highly irritating hydrocarbon which has often been used to create experimental cancers. The method of administering the carcinogen isn't clearly described: "Local exposure of carcinogen…in the cervical canal for 9 weeks…induced one invasive carcinoma in the vagina-exocervix and five in the endocervix." It was introduced into the cervical canal, but in what form and how often isn't described. Methylcholanthrene has some estrogenic properties.

Estrogen increases the production of mucus in the cervix and vagina, and increases its water content and mobility. Abundant and fluid mucus has a cleaning action, eliminating bacteria and other material. Progesterone makes the mucus more viscous and less hydrophilic, and when it dominates the reproductive physiology, it effectively creates a plug in the cervix that prevents the entry of sperms.

The choice of the cervix and vagina suggests that the authors were "engineering" the experimental outcome, because the effect of progesterone on cervical mucus is very well known. To apply the irritant to an area where it would normally be washed away by the mucus, but where it is kept in place by hormonally altering the mucus, is really a way of manipulating how much exposure to the irritating chemical the tissue will receive. It's analogous to studying the "toxicity" of an antihistamine, by applying a toxin to the nasal membrane of a person with a cold, and then administering the antihistamine to stop the flow of mucus, allowing the membrane to fully absorb the applied dose of toxin.

A different chemical carcinogen, 7,12-dimethylbenz(a)anthracene was used in another 1973 study,[10] in combination with progesterone. In this experiment, the carcinogen was administered to rats in one dose by stomach tube, dissolved in corn oil. The progesterone was injected subcutaneously in 3 mg doses in corn oil three times per week. Unfor-

tunately, there was no control group in which the corn oil was injected alone.

The progesterone was supposedly dissolved in the corn oil, one tenth ml per dose. That amount of progesterone (3 % weight/volume) will dissolve in hot corn oil, but as the oil cools, the progesterone crystallizes and precipitates. That creates doubt regarding what the animals were actually receiving.

Corn oil is one of the most effective vegetable oil tumor promoters/carcinogens, and it's now considered improper to use it as a solvent for testing even oral carcinogens, since some chemicals that are carcinogenic in the oil are relatively harmless when administered without the corn oil. The animals got 2 mL of corn oil in the stomach feeding with the carcinogen. One of the groups (group 5) received, in addition, more than 6 mL of corn oil in the injections. The experiment lasted only 135 days, and in the group that received only the carcinogen, the mortality was only 5 %, and that death occurred shortly after the carcinogen was administered. All of the groups receiving the corn oil and progesterone injections had higher mortality, two with 25 %, one with 37.5 % mortality. Despite the unexplained general problem with prematurely dying rats, the authors found that "The relative incidence rates indicated that pretreatment with progesterone inhibited tumorigenesis, except in the group (5) in which progesterone treatment was continued for the duration of the experiment." Without progesterone, it is almost certain that the additional corn oil injected would have increased tumorigenesis in all experimental groups.

Without that vehicle control group, the experiment can just as well be described as a test of corn oil, rather than of progesterone. If you claim to be testing the capacity of a substance to promote tumors, it shouldn't be administered in a standard tumor promoter.

A 1968 publication by Glucksmann and Cherry was included in the documents offered as evidence of progesterone's carcinogenicity. Unfortunately, they neglected to identify the vehicle used for giving twice weekly intramuscular injections of 1 mg of progesterone, and they didn't have a vehicle control for the progesterone injections. At that time, the most common vehicle was a mixture of 9 % benzyl alcohol and oil, usually sesame or peanut oil. Benzyl alcohol by itself is quite toxic, and was responsible for the death or brain damage of thousands of babies in hospitals, even in the small amounts that remained as residue

in tubing after they had been rinsed with "bacteriostatic water," which contains 0.9 % benzyl alcohol, and which is still used as the vehicle for many injections, such as penicillin and vitamin B_{12}. The antitoxic (or "catatoxic") action of progesterone greatly reduces the toxicity of benzyl alcohol.

In discussing the effects of hormones on the induction of sarcomas, Glucksmann and Cherry comment that "The rate of induction of sarcomas in intact rats was slowed down slightly by treatment with progesterone and not significantly increased in spayed animals…"

In their Discussion section, they mention several previous studies in relation to their own results, and comment, regarding other studies, that "The effect of progesterone on the type of induced cervical cancer in mice consists in increasing the columnar component of mixed carcinomas in castrates…without materially affecting the induction period and tumour yield. Thus the experimental evidence in rats and mice is not as clearly antitumorigenic as that ofLipschutz[11] for guinea pigs and the clinical observations.[12,13]"

Comparing this study to that of Burrows and Hoch-Ligetti, the dose of 2 mg per week per rat is lower, on a body-weight basis, than the earlier study's dose of 1 mg/week in mice, but the greater frequency came a little closer to the continuous treatment that Lipschutz said was necessary. This could account for the fact that some of their results were intermediate between those of the Lipschutz group and those of Burrows and Hoch-Ligetti.

In Glucksmann's and Cherry's results, progesterone retarded one type of tumor and appeared to promote another (an epithelial tumor, which wasn't described as malignant or cancerous), but if the progesterone was dissolved in a tumor promoting solvent, it's impossible to ascribe the effect to progesterone. Vegetable oil applied to epithelium that has been exposed to a carcinogen such as the DMBA they used will typically increase the growth of the tumors. Without information about the vehicle, it's impossible to interpret that part of their results clearly, but anyway, they didn't describe any carcinogenic effect of progesterone; they did, however, describe a clearly anticarcinogenic action.

A 1962 study, by Capel-Edwards, et al., was intended to compare the effects of prolonged administration of high doses of progesterone with the known toxic effects of synthetic progestagens. They didn't find any malignant tumors, so the study can't be taken as evidence of

the carcinogenicity of progesterone. The vehicle used for dissolving the progesterone consisted of benzyl alcohol, ethanol, and ethyl oleate. Some of the solutions contained more than 10 % progesterone. When this sort of solution interacts with water in the tissues, it causes the progesterone to crystallize out of solution. The authors reported that "subcutaneous tissue reactions developed at injection sites," and that these "occurred in all animals, including controls, and were apparent for several days after the injection." These injection-site lesions sometimes developed into "sterile abscesses which eventually ulcerated and healed." The only dog that died during the study was in the control group, and although there were "a number of pathologic findings," the exact nature of that dog's sickness couldn't be determined. The injections were given daily, for a total of 518 injections in each animal, and each injection contained as much as 4 mL of the vehicle. Almost an ounce per week of this material, combined with the massive irritation produced by crystallization at hundreds of injection sites, would be the most likely explanation for the various inflammatory changes they saw, including osmotic fragility of red blood cells, and as much as a 50 % enlargement of liver and kidneys.

Although some of the basic ideas about canine physiology that were held when the Capel-Edwards study was designed have been found to be mistaken, and the toxicity of their vehicle can now be seen, and they didn't conclude that progesterone was carcinogenic, their study wasn't the worst of those that have been presented as evidence of progesterone's carcinogenicity.

When an experimenter doesn't yet have a clear hypothesis, it's reasonable to do some exploratory tests, just to get an orientation to the possibilities so that it's possible to form a well defined hypothesis, before designing an experiment that will test the hypothesis. Sometimes an experimenter and journal editors will allow a merely exploratory experiment to be published. If they don't draw inappropriate conclusions from the ambiguous results, the publication can be justified, simply because it might stimulate others to investigate the subject more thoroughly.

But often editors allow the author to draw conclusions from the experiment that are not directly implied by the data, especially when those conclusions support the editor's prejudices. A conclusion may be consistent with, though not implied by, the results of the experiment. These publications may be effective propaganda, but they aren't good science.

But California's OEHHA identifies those eight publications as "the relevant evidence that clearly shows through scientifically valid testing according to generally accepted principles that progesterone causes cancer."

In 2004, the agency was petitioned to remove progesterone from the list. In the document rejecting that petition, they mentioned that IARC in 1999 had reviewed newer evidence confirming the carcinogenicity of progesterone. After months of asking the man in charge of rejecting the petition to identify that very important new data, I hadn't received an answer, so I wrote to IARC, and the man in charge there responded:

"The IARC (1999) review is actually an IARC Monographs volume (Vol. 72) …This volume focuses on contraception and post-menopausal therapy. Progesterone is not used for these indications and, hence, after a quick search in the book I found only one reference that clearly reports an experiment with progesterone." (Wednesday, October 04, 2006 12:44 AM)

That article (Grubbs CJ, Peckham JC & McDonough KD (1983) Effect of ovarian hormones on the induction of 1-methyl-1-nitrosourea-induced mammary cancer. Carcinogenesis 4(4):495-497) reported that progesterone reduced the incidence of mammary cancers caused by a carcinogen administered in vegetable oil.

I don't think it's possible that anyone could read articles like this, that don't even claim to show that progesterone causes cancer, and conclude that they provide evidence of progesterone's carcinogenicity. The choice of "evidence" seems to have been a selection of titles of unread articles. And even the title of the 1999 IARC volume would have suggested to most people that it wasn't a review of progesterone.

The lack of vehicle controls in some of the studies, the use of an unnamed vehicle in one beagle study, and the use of tumor-promoting vehicles in most if not all of the studies, means that no scientifically competent or valid studies have been cited by IARC, NTP, or the California state bureaucracy, OEHHA, to support California's claim that they know progesterone is a carcinogen.

In their 2004 document, OEHHA mentioned 17 articles that had been submitted regarding progesterone's protective effects. Some of these were identified; two were egregiously misrepresented in a single sentence:

Plu-Bureau, et al., were said to have reported "no association between breast cancer risk and progesterone topically applied for the treatment of mastalgia and benign breast disease…" What Plu-Bureau, et al., said immediately following that was "Although the combined treatment of oral progestogens with percutaneous progesterone significantly decreased the risk of breast cancer (RR = 0.5; 95 % confidence interval 0.2-0.9) as compared with nonusers, there was no significant difference in the risk of breast cancer in percutaneous progesterone users versus nonusers among oral progestogen users." (RR means "relative risk," or "risk ratio," and 0.5 means a 50 % reduction in risk.)

Cowan, et al.,[14] according to the OEHHA document, reported "reduced premenopausal breast cancer in women who had a history of progesterone deficiency." What they actually said was "These women were categorized as to the cause of infertility into 2 groups, those with endogenous progesterone deficiency (PD) and those with nonhormonal causes (NH). Women in the PD group had 5.4 times the risk of premenopausal breast cancer as compared to women in the NH group. This excess risk could not be explained by differences between the 2 groups in age at menarche or age at menopause, history of oral contraceptive use, history of benign breast diseases, or age at 1st birth. Women in the PD group also experienced a 10-fold increase in deaths from all malignant neoplasm compared to the NH group."

Ending the paragraph that mentioned those studies, the California document continues: "However, there is also evidence that progesterone may have a mitogenic effect. For example, Soderqvist et al.[15] found that in breast cells of healthy women, cell proliferation was correlated with serum progesterone levels, thereby suggesting a proliferative action of progesterone."

Such a suggestion is not made by that "correlation." The authors said, "Our objective was to assess proliferation in normal breast epithelial cells from healthy women during the follicular and luteal phases of the menstrual cycle." At the beginning of the luteal phase, both estrogen and progesterone normally rise several-fold, so the small increase in proliferative rate also correlates with estrogen levels. A "defective luteal phase" is common, in which the ratio of estrogen to progesterone is high, and in that case progesterone's well established antiproliferative, differentiative effect will be overridden by estrogen's proliferative stimulation.

The state's reviewers didn't comment on the studies which showed that progesterone, besides inhibiting proliferation, also inhibits an "oncogene" which is associated with cancer, rather than just with proliferation. Instead, they cited a meaningless "correlation" as if it were some kind of argument against progesterone's anticancer effects. The authors of this document don't seem to know very much about the biology of cancer, but maybe they know too much about the issue of the proliferation of breast epithelium.

In a paragraph "rebutting" the petitioner's point that "This new research supports that exogenous progesterone actually reduces the risk of breast cancer in humans," the authors don't mention that point at all, but instead refer to cancer treatment and to the various claims relating to progesterone's carcinogenicity, ending with the mention of "studies that suggest progesterone stimulates cell proliferation.[15]" Apparently the authors had no answer to the petitioners' point, and preferred to talk about proliferation of breast cells.

Nearing the end of the document, the authors say "The NCI also reports on other studies of estrogens with progestins, which would suggest that progesterone increases the risk of human breast cancer," and then quotes comments on studies of estrogens with (synthetic) progestins. The authors cite two more studies with synthetic progestins, and then say "As discussed above, the mammary gland was a main target site in animal cancer bioassays providing the basis for the IARC and NTP identification of progesterone as carcinogenic." (The preceding discussion had mentioned the 4 year beagle study—which ended the careers of the researchers—and a 1993 publication by Kordon, et al.,[16] which had no control group for reference, and instead compared progesterone with different doses of medroxyprogesterone acetate, finding that the fewest tumors occurred in the progesterone group.[†])

The techniques of distortion, diversion and evasion in this document are so obvious that any college composition teacher would have returned it to the student for revision. The document says much more about its authors than about its subject.

I think this bureaucratic behavior is understandable only if you know the composition of the group that is responsible for the progesterone listing, because the proliferation of breast cells has become an important issue for the group around USC professor Malcolm Pike.

Around 1980, Malcolm Pike, a statistician from South Africa, working in epidemiology, began arguing that the use of oral contraceptives prevented cancer. This epidemiologist, unfamiliar with steroid physiology except as it filtered through the oral contraceptive industry, decided that progesterone was the primary cause of breast cancer, by stimulating cell division and increasing the tissue density of the breast.

This line of reasoning gained adherents in the USC Keck School of Medicine, despite an overwhelming amount of contrary evidence, accumulated over more than 50 years, that progesterone protects against breast cancer, partly by inhibiting cell division, and that increased breast density is significantly associated with breast mitogens, such as serum insulin-like growth factor-I (IGF), prolactin, and estrogens, rather than with progesterone.

Breast mitogens correspond to both breast density and the risk of breast cancer (Boyd), but progesterone (antimitogen) corresponds to factors associated with low risk of breast cancer. Progesterone may reduce breast density by inhibiting some growth factors, including IGF, NO (nitric oxide), VEGF (vascular endothelial growth factor), bcl-2 (a protein that inhibits apoptosis), polyamines, and prostaglandins.

Much of the research at USC's Keck School has been generously funded by pharmaceutical companies with huge interest in estrogen-related products. The medical school website has articles by their faculty that give the impression that they are often more concerned with the fate of the estrogen market than with the science they claim to be doing. For example, commenting on the WHI evidence showing that estrogen helps to cause Alzheimer's disease, professor B.E. Henderson said "I continue to believe that estrogen therapy may help reduce a woman's risk of developing Alzheimer's disease…" I noticed that there were hundreds of other estrogen-related items on the USC website.

The medical school, some of its professors, government agencies, and private companies are involved in some very complex, overlapping activities that give the impression of what used to be called "conflicts of interest."

The Keck School (a private institution), and the company, Balance Pharmaceuticals, Inc., controlled by three of their professors, participate in the business promotion organization operated by the State of California, Larta Institute, which manages Project T_2, which is part of a "commercialization" system, involving awards of federal government

money: "The organization will provide the awardees with assistance in all aspects of commercialization, including business development, funding and capital acquisition, government regulatory processes, intellectual property protection, licensing strategies, and merger and acquisition opportunities. SBIR Phase II is the research and development stage of the well-known program, with award sizes typically starting at $750,000 each." "Working with one of the Federal government's largest and most important agencies to assist SBIR awardees on the cusp of commercialization is a natural extension of everything we've done for the past ten years," said Larta Institute CEO Rohit Shukla.

Besides the issue of giving public money to private groups to commercialize ideas, many of which were developed using government-funded research, adding assistance with "government regulatory processes" to the help given to private corporations should arouse suspicions. The idea of "privatization" is given a new dimension: It's all for the insiders, without the usual lip-service paid to "competition."

On California's committee that chooses chemicals to put on their list of "known carcinogens" is Juliet Singh, who is the chief executive of Trans Pharma Corporation, a company that is developing transdermal drug delivery systems, for example for giving hormones by applying them to the skin. Under California's law, chemicals on the carcinogen list may to sold as drugs without a warning.

On the committee with Singh are Anna Wu and Thomas Mack, who co-authored several papers with Malcolm Pike, who was the most visible promoter of the campaign against progesterone, and who with two other USC professors controls Balance Pharmaceuticals, Inc., which is being promoted by Larta Institute, and that's planning to market a contraceptive based on the idea of suppressing progesterone. Three USC professors are on California's carcinogen committee, more than from any of the other universities in the state.

In a jury trial, I think this would look like a tainted jury.

Comparing the California agency's parody of legitimate process in this instance with its reconsideration in 2002 of its listing of saccharin as a carcinogen is illuminating. In that case, there was at least a pretense that the staff had made an attempt to provide "all relevant scientific evidence" for the committee to review, as specified by the agency's regulations. And in its decision, the State's Qualified Experts made a point of declaring, according to the language of the law, that in the opinion

of the state's qualified experts it had not been "clearly shown through scientifically valid testing according to generally accepted principles to cause cancer." The Committee found that, in this case, it had to use a "weight of evidence" approach to evaluate the body of information available…

Unfortunately, the committee allowed some bizarre speculations about calcium phosphate to outweigh the fact that saccharin is a mild carcinogen, and in evaluating the rat experiments they were in such a hurry to remove saccharin from the list that they neglected to notice that calcium phosphate precipitation isn't unique to rat urine, but very commonly occurs in human urine. Their decision to remove it from the list rested on that non-fact.

Although the agency cited 150 studies, and went through the formality of describing some of them in their document, anyone reading the document justifying the delisting of saccharin, and the document rejecting the delisting of progesterone, will find it hard to see a principle of law that could justify removing a carcinogen from the list, because of uncertainty regarding the mechanism by which it causes cancer, and keeping progesterone on the list, despite overwhelming evidence that it protects against cancer, and a great amount of evidence regarding the mechanisms through which the protection occurs.

The committee of experts who "weighed" speculations about calcium phosphate in the 2002 saccharin document, chose not to consider, either in 1987 or 2004, any of the hundreds of empirical studies showing progesterone's protective anticancer effects. The committee "considered" approximately half of all research publications on saccharin and cancer, and fewer than 1 % of those relating to progesterone and cancer. Something other than scientific objectivity must explain those differences.

The agency in charge of those processes of evaluating evidence of carcinogenicity declines to identify the people who made those possibly biased, certainly bizarre, selections of articles, or to list their qualifications for being in the crucial position of deciding what evidence would be provided to the Scientific Advisory Panel. And in the list of studies that the committee did receive, are two (Kwapien, et al., and Yager and Yager) that are about completely different chemicals, that the agency still identifies as evidence of progesterone's carcinogenicity.

Many progesterone products have been taken off the market because of California's warning signs and labels, and as a result many women are

having to rely on their physicians for progesterone. Too many physicians know only what the pharmaceutical companies want them to know about progesterone and other hormones that had been available for decades in places such as health food stores.

An article in JAMA (Marcia Stefanick, April 11, 2006) was summed up by Stefanick in a way that seems designed to encourage physicians to return to prescribing estrogen: "In the estrogen and progestin trial those women who got on the active pills, we saw an increase in breast cancer within five years. In the case of estrogen only, we not only do not see an increase by 7 years, but there's actually a suggestion of a decrease." That is a serious misrepresentation of the study.

The recently reported (December 15, 2006) decline of breast cancer incidence, coinciding with the great decrease in the use of menopausal estrogen treatments, also coincided with an increased use of natural progesterone, but if the lawyers, bureaucrats, and agents of the estrogen industry succeed in convincing the public that progesterone is carcinogenic, its use will decline, and breast cancer incidence could be expected to increase again.

The studies that show cancer prevention by progesterone have, over the years, failed to resonate in the medical culture. The confusion created by classifying the antiprogestational, carcinogenic synthetics as "progestins" is largely responsible for the failure to understand the protective nature of progesterone.

If the evidence showing that progesterone prevents or cures cancer could be weighed against the evidence purporting to show that it is carcinogenic, I think it would be clear that something like a cultural-commercial misogyny has been at work. The novelty of the newer misogyny is that it is so often led, or at least figureheaded by women.

† Compare the results of Kordon, et al., 1993, with the later results of Aldaz, et al., 1996: Kordon, et al., reported 58 % of the animals had tumors in the group receiving low dose MPA pellets, 98 % in the high dose MPA group.
Aldaz, et al.,[17] wrote "The synthetic progestin medroxyprogesterone acetate (MPA) was postulated by some authors to increase mammary tumor incidence in various rodent models. However, controversy exists regarding the role of MPA in experimental and human carcinogenesis." "MPA by itself did not produce any mammary tumors."

Estrogen and Brain Aging in Men and Women

Depression, Energy, Stress

Ray Peat's Newsletter, 2009

ALTHOUGH the incidence of Alzheimer's disease is 2 or 3 times as high among women as among men, there is a major campaign under way to convince the public that taking estrogen supplements will prevent the disease. Estrogen is now mainly promoted to prevent osteoporosis (another problem that is more common in women) and heart disease (which is more common in men).

This substance, which came into medical use as "the female hormone" for the treatment of "female problems," especially for improving fertility, and then for preventing fertility as the oral contraceptive, is now being aimed primarily at the post-reproductive population, for problems that are essentially unrelated to femininity. It is, in fact, being presented to the public as something to prevent major age-related conditions.

Brain degeneration, like osteoporosis, takes years to develop. Analysis of letters written by young women, for example, showed limited mental functioning in those who many years later developed Alzheimer's disease, and young women who have small bones are the ones most likely to develop osteoporosis later. It seems clear that the course of degenerative aging processes is set in young adulthood (or even earlier), and that it is never too early to be concerned with correcting processes that are going in the wrong direction.[1,2]

In "The Biological Generality of Progesterone" (1979) I proposed that the life-long trajectory of energy production and longevity was strongly influenced by prenatal nutrition and progesterone. This idea was based on work by people such as Marion Diamond, who showed that prenatal progesterone enlarges the cortex of the brain, and that estrogen makes it smaller, and Leonell Strong, who showed that a treatment that lowered the estrogen function in a young mouse could produce cancer-free offspring for several generations. Strong's work was very encouraging, because it showed that biological problems that had been "bred in" over many generations could be corrected by some simple metabolic treatments.

Seeing these profoundly toxic long-range effects of estrogen, which shaped the animal's growth, development, function, and even its hered-

ity, made it important to learn how estrogen works, because such fundamental changes covering the whole range of biology, produced by a simple little molecule, promised to reveal interesting things about the nature of life.

Aging is an energy problem, and in the brain, which has extremely high energy requirements, interference with the energy supply quickly causes cells to die.

I believe that estrogen's "principle," in all of its actions, is to interfere with the respiratory mode of energy production. This is an integrating principle that explains estrogen's immediate, direct effects on cells and organisms, which aren't explained by the idea that it acts on the genes through a specific "estrogen receptor." (It's hard to imagine, for example, how the "estrogen receptor" doctrine could explain the fact that a single injection of estrogen can kill a large portion of brain cells.) It explains why estrogen causes cells to take up water, allowing calcium to enter, activating various enzymes and cell division. On the organismic level, it explains why estrogen mimics "shock," releasing histamine and activating the nervous and glandular stress response system. The inefficiency of metabolism which doesn't use oxygen in the normal way causes glucose to be used rapidly, and this in itself is enough to trigger the release of pituitary ACTH and adrenal cortisol. The ACTH, and related hormones, liberate free fatty acids, which cells take up instead of glucose, and this (in the so-called Randall cycle) further limits the body's ability to oxidize glucose.

People have spoken of "cascades" in relation to the adrenal glucocorticoids (e.g., cortisol) and estrogen, leading to cell damage, but really both of these hormonal cascades have to be seen as part of a more general collapse of adaptive systems, as a result of both chronic and immediate inadequacies of energy production.

Estrogen activates the adrenal stress reaction by way of the hypothalamus and pituitary, by direct actions on the adrenal glands, and by a variety of indirect effects, such as the increase of free fatty acids. It activates the excitotoxic glutamic acid pathway, and interferes with protective adenosine inhibition of nerves. It has both direct and indirect ways of promoting the formation of nitric oxide and carbon monoxide. These, and other estrogen-promoted factors, quickly and seriously interfere with mitochondrial respiration. Many of these effects contribute to

increased intracellular calcium and free radical production, contributing to both the excitatory excess and the energy deficit.

The biochemical details of these cascades are mainly interesting because they show how many different kinds of stress converge on a few physiological processes—mitochondrial energy production, cellular excitation, and intercellular communication—which, when damaged thousands of times, lead to the familiar states of old age. These few functions, damaged by an infinite variety of stresses, have their own complexly adaptive ways of deteriorating, producing the various degenerative diseases.

This perspective brings dementia, heart failure, autoimmunity, immunodeficiency and other diseases of aging together, in ways that allow generalized therapeutic and preventive approaches.

The antistress, antiestrogen approaches become fundamental to prevention of aging.

The pro-estrogenic nature of the unsaturated fatty acids is probably the biggest barrier to the radical elimination of degenerative diseases. Various saturated fatty acids, including butyric, octanoic, and palmitic, have protective effects on mitochondrial respiration.

Progesterone is the basic brain-protective antiestrogen. It works to protect the brain at many levels (preventing lipid peroxidation, exitotoxicity, nitric oxide damage, energy deficit, edema, etc.) and it promotes repair and recovery.

Progesterone in most cases has effects opposite to estrogen's, improving mitochondrial energy production while preventing excessive excitation. Along with pregnenolone, progesterone is recognized as a neurosteroid with anti-excitotoxic actions, with the ability to promote repair and regeneration of the nervous system. (Roof, Stein, Faden; Schumacher, et al.; Baulieu.)

The use of aspirin, which reduces inflammation and inhibits the formation of neurotoxic prostaglandins, is known to be associated with a lower incidence of Alzheimer's disease, and in other contexts, it offers protection against estrogen. Naloxone, the antiendorphin, has been found to reverse some of the cumulative effects of stress, restoring some pituitary and ovarian function, and it promotes recovery after brain injury; in a variety of ways, it corrects some of estrogen's toxic effects.

Adenosine helps to maintain brain glycogen stores, which are lost in stress and aging. Vitamin B_{12} protects against nitric oxide, and improves alertness.

Pyruvic acid has brain-protective effects, apparently through its decarboxylation (producing carbon dioxide) rather than through its use as an energy source, since other ketoacids are similarly protective. (The ketoacids occur in some natural foods.) The directly brain-protective effect of carbon dioxide offers many clues that should be interpreted in relation to estrogen's toxicity, since many of their effects on nerves are opposite. Estrogen blocks the production of energy while it stimulates nerve cells to use energy more rapidly, and carbon dioxide promotes the production of energy, while restraining the excitation which expends energy. The presence of carbon dioxide is an indicator of proper mitochondrial respiratory functioning.

Pharmaceutical blockers of glutamic acid transmission, and of calcium and sodium uptake, prevent some deterioration following brain injury, but the most physiological way to protect against those toxic processes is to maintain metabolic energy at a high level. Magnesium, which is protective against excitatory damage and is a calcium antagonist, tends to be retained in proportion to the activity of thyroid hormone.

As I have discussed previously, progesterone alone has brought people out of post-epileptic dementia and senile dementia, but it is reasonable to use a combined physiological approach, including thyroid.

Besides providing new insights into biological energy and aging, the recognition that estrogen activates the stress hormone system—the pituitary-adrenal system—also provides clear insights into other problems, such as the polycystic ovary syndrome, hirsutism, adrenal hyperplasia, Cushing's disease, etc.

Estrogen and Osteoporosis

Ray Peat's Newsletter, 2006

> "How does estrogen enhance endotoxin toxicity? Let me count the ways.[1]"
>
> — J. J. Maher

THE government declared victory in the war on cancer, though the age-specific death rate from cancer keeps increasing. In the equally well publicized effort to prevent disability and death from osteoporosis, no one is declaring victory, because the only trend in its incidence that has been reported is an increase. The estrogen-promoting culture tells us that this is because of the aging of the population, but the age corrected numbers still show a great increase—for example, in Finland between 1970 and 1995, the number of women (for a given population of women older than 60) breaking their forearm because of osteoporosis more than doubled.[2] That this happened during a time when the use of estrogen had become much more common doesn't present a good argument for the protective effects of estrogen treatment. (And during this period there was a large increase in the consumption of estrogenic soy products.) Recently our local newspaper had a story at the bottom of the front page reporting that lean women who used estrogen and synthetic progestins had an 80 % higher rate of breast cancer. Several days later, across the top of the front page, there was a rebuttal article, quoting some doctors including a "world class expert on hormone replacement therapy" and a woman who has taken Premarin for forty years and urges everyone to take it. The "protection against osteoporosis" and against heart disease, they said, must be weighed against a trifle such as the 80 % increase in cancer. It appeared that the newspaper was apologizing for reporting a fact that could make millions of women nervous.[3]

Medical magazines, like the mass media, don't like to miss any opportunity to inform the public about the importance of using estrogen to prevent osteoporosis. Their attention to the bone-protective effect of progesterone has been noticeably less than their mad campaign to sell estrogen, despite the evidence that progesterone can promote bone rebuilding, rather than just slowing its loss. Although I have spoken

about progesterone and osteoporosis frequently in the last 25 years, I have only occasionally considered what estrogen does to bones; generally, I described estrogen as a stress-promoting and age-promoting hormone. In the 1970s, pointing out progesterone's protective antagonism to excessive amounts of other hormones, and that the catabolic glucocorticoids tend to increase with aging, I began referring to progesterone as the "anticatabolic" hormone that should be used to prevent stress-induced atrophy of skin, bones, brain, etc.

A former editor of *Yearbook of Endocrinology* had reviewed a series of studies showing that excess prolactin can cause osteoporosis. Then, he presented a group of studies showing how estrogen promotes the secretion of prolactin, and can cause hyperprolactinemia. In that review, he wryly wondered how something that increases something that causes osteoporosis could prevent osteoporosis.

Women have a higher incidence of osteoporosis than men do. Young women have thinner more delicate bones than young men. The women who break bones in old age are generally the women who had the thinnest bones in youth. Menstrual irregularities, and luteal defects, that involve relatively high estrogen and low progesterone, increase bone loss.

Fatter women are less likely to break bones than thinner women. Insulin, which causes the formation of fat, also stimulates bone growth. Estrogen however, increases the level of free fatty acids in the blood, indicating that it antagonizes insulin (insulin decreases the level of free fatty acids), and the fatty acids themselves strongly oppose the effects of insulin. Estrogen dominance is widely thought to predispose women to diabetes.

Between the ages of 20 and 40, there is a very considerable increase in the blood level of estrogen in women. However, bone loss begins around the age of 23, and progresses through the years when estrogen levels are rising. Osteoarthritis, which involves degeneration of the bones around joints, is strongly associated with high levels of estrogen, and can be produced in animals with estrogen treatment.

Thirty years ago, when people were already claiming that estrogen would prevent or cure osteoporosis, endocrinologists pointed out that there was no x-ray evidence to support the claim. Estrogen can cause a positive calcium balance, the retention of more calcium than is excreted, and the estrogen promoters argued that this showed it was being stored in

the bones, but the endocrine physiologists showed that estrogen causes the retention of calcium by soft tissues. There are many reasons for not wanting calcium to accumulate in the soft tissues; this occurs normally in aging and stress.

Then, it was discovered that, although estrogen doesn't improve the activity of the cells that build bone, it can reduce the activity of the cells that remove bone, the osteoclasts. The osteoclast is a type of phagocytic cell, and is considered to be a macrophage, the type of cell that can be found in any organ, which can eat any sort of particle, and which secretes substances (cytokines, hormone-like proteins) that modify the functions of other cells. When estrogen was found to impair the activity of this kind of cell, there wasn't much known about macrophage cytokines.

With the clear evidence that estrogen inhibits the osteoclasts without activating the bone-building osteoblasts, estrogen was said to "prevent bone loss," and from that point on we never heard again about estrogen promoting a positive calcium balance. Calcium retention by soft tissues has come to be an accepted marker of tissue aging, tissue damage, excitotoxicity, and degeneration. Positive calcium balance had been the essence of the argument for using estrogen to prevent osteoporosis: "Women are like chickens, estrogen makes them store calcium in their bones." But if everyone now recognizes that calcium isn't being stored in bones, it's better for the estrogen industry if we forget about the clearly established positive calcium balance produced by estrogen.

The toxic effects of excessive intracellular calcium (decreased respiration and increased excitation) are opposed by magnesium. Both thyroid and progesterone improve magnesium retention. Estrogen dominance is often associated with magnesium deficiency, which can be an important factor in osteoporosis.[4,5] As part of the campaign to get women to use estrogen, an x-ray (bone density) test was devised which can supposedly measure changes in the mineral content of bone. However, it happens that fat and water interfere with the measurements. Estrogen changes the fat and water content of tissues. By chance, the distortions produced by fat and water happen to be such that estrogen could appear to be increasing the density of a bone, when it is really just altering the soft tissues. Ultrasound measurements can provide very accurate measurements of bone density, without the fat and water artifacts that can produce misleading results in the x-ray procedure, and don't expose the patient to radiation, but the ultrasound method is seldom used.

In recent years, there has been quite a lot of research into the effects of the macrophage cytokines. Immune therapy for cancer was considered quackery when Lawrence Burton identified some substances in blood serum that could cause massive tumors in rodents to disappear in just a few hours. One of the serum factors was called Tumor Necrosis Factor, TNF. An official committee was formed to evaluate his work, but it reported that there was nothing to it. A member of the committee later became known as "the authority" on tumor necrosis factor, which was thought to have great potential as an anticancer drug. However, used by itself, TNF killed only a few cancers, but it damaged every organ of the body, usually causing the tissues to waste away. Other names, lymphotoxin and cachectin, reflected its toxic actions on healthy tissues.

Aging involves many changes that tend to increase the inflammatory reaction, and generally the level of TNF increases with aging. Although cancer, heart failure, AIDS, and extreme hormone deficiency (from loss of the pituitary or thyroid gland, for example) can cause cachexia of an extreme and rapid sort, ordinary aging is itself a type of cachexia. Progeria, or premature aging, is a kind of wasting disease that causes a child's tissues (including bones) to atrophy, and to change in many of the ways that would normally occur in extreme old age.

Recent studies have found that both men and women lose minerals from their bones at the rate of about 1 % per year. Although men have lower estrogen in youth than women do, their bones are much heavier. During aging, as their bones get thinner, men's estrogen levels keep rising.

Besides having weaker bones, old people have weaker muscles, and are more likely to injure themselves in a fall because their muscles don't react as well. Muscle loss occurs at about the rate of 1 % per year.

Women's muscles, like their bones, are normally smaller than men's, and estrogen contributes significantly to these differences.

TNF can produce very rapid loss of tissue including bone, and in general, it rises with aging. Some of the people who like to say that "osteoporosis is caused by estrogen deficiency" know about the destructive actions of TNF, and argue that it rises at menopause "because of estrogen deficiency." There are very good reasons for rejecting that argument; the experiments sometimes seem to have been designed purely for propaganda purposes, using toxic levels of estrogen for a specific result.

One researcher noted that the effects of estrogen on cells *in vitro* are biphasic: Low doses increased TNF, high doses decreased TNF. Everyone knows that unphysiologically high doses (50 or 100 or more times above the physiological level of around 0.25 μg/L) of estrogen are toxic to cells, producing functional and structural changes, and even rapid death. So, when a researcher who wants to show estrogen's "bone protective" effect of lowering TNF adds a lethal dose of estrogen to his cell culture, he can conclude that "estrogen inhibits TNF production." But the result is no more interesting than the observation that a large dose of cyanide inhibits breathing.

TNF is produced by endotoxin, and estrogen increases the amount of endotoxin in the blood. Even without endotoxin, though, estrogen can stimulate the production of TNF. Lactic acid and unsaturated fats and hypoxia can stimulate increased formation of TNF. Estrogen increases production of nitric oxide systemically, and nitric oxide can stimulate TNF formation. How does TNF work, to produce tissue damage and wasting? It causes cells to take up too much calcium, which makes them hypermetabolic before it kills them. It increases formation of nitric oxide and carbon monoxide, blocking respiration. TNF can cause a 19.5 fold increased in the enzyme which produces carbon monoxide,[6] which blocks respiration.

All of the normal conditions associated with high estrogen also are found to involve increased production of TNF, and treatment of animals with estrogen clearly increases their TNF. Premature ovarian failure (with low estrogen levels) leads to reduced TNF, as does treatment with antiestrogens. If bone resorption is significantly regulated by TNF, then it should be concluded that increased estrogenic influence will tend to produce osteoporosis.

Tamoxifen, which has some estrogenic effects, including the inhibition of osteoclasts, can kill osteoclasts when the dose is high enough. The inhibition of osteoclast activity by either estrogen or tamoxifen is probably a toxic action, that has been characterized as "beneficial" by the estrogen industry simply because they didn't have any better argument for getting women to use their products.

Some types of dementia, such as Alzheimer's disease, involve a life-long process of degeneration of the brain, with an inflammatory component, that probably makes them comparable to osteoporosis and muscle-wasting. (In the brain, the microglia, which are similar to

macrophages, and the astrocytes, can produce TNF.) The importance of the inflammatory process in Alzheimer's disease was appreciated when it was noticed that people who used aspirin regularly had a low incidence of that dementia. Aspirin inhibits the formation of TNF, and aspirin has been found to retard bone loss. In the case of osteoporosis,[7] as in Alzheimer's disease, the incidence is two or three times as high in women as in men. In both Alzheimer's disease and osteoporosis, the estrogen industry is arguing that the problems are caused by a suddenly developing estrogen deficiency, rather than by prolonged exposure to estrogen.

Similar arguments were made fifty years ago regarding the nature of the menopause itself—that it was caused by a sudden decrease in estrogen production. The evidence that has accumulated in the last forty years has decisively settled that argument: Menopause is the result of prolonged exposure to estrogen. (Even one large dose destroys certain areas in the brain, and chronic, natural levels damage the nerves that regulate the pituitary. Overactivity of the pituitary leads to many other features of aging.)

The links between estrogen and TNF appear to be essential factors in aging and its diseases. Each of these substances has its constructive, but limited, place in normal physiology, but as excitatory factors, they must operate within the appropriate constraints. The basic constraint is that resources, including energy and oxygen, must be available to terminate their excitatory actions. Adequate oxygen, a generous supply of carbon dioxide, saturated fats, thyroid, and progesterone restrain TNF, while optimizing other cytokines and immune functions, including thymic protection. In the development of the organism and its adaptive functions, there are patterned processes, functional systems, that can clarify the interactions of growth and atrophy. The respiratory production of energy and carbon dioxide, and the respiratory defect in which lactic acid is produced, correspond to successful adaptation, and to stressful/excitotoxic maladaptation, respectively. Excitotoxicity, and Meerson's work on the protective functions of the antistress hormones, have to be understood in this framework. This framework integrates the understanding of cancer metabolism with the other stress metabolisms, and with the metabolism of normal growth.

Unsaturated fats, iron, and lactic acid are closely related to the actions and regulation of TNF, and therefore they strongly influence the nature of stress and the rate of aging.

The fact that cancer depends on the presence of polyunsaturated fats probably relates to the constructive and destructive actions of TNF: The destructive effects such as multiple organ failure/congestive heart failure/shock-lung, etc., apparently involve arachidonic acid and its metabolites, which are based on the so-called essential fatty acids. When oxygen and the correct nutrients are available, the hypermetabolism produced by TNF could be reparative,[8] rather than destructive. Stimulation in the presence of oxygen produces carbon dioxide, allowing cells to excrete calcium and to deposit it in bones, but stimulation in the absence of oxygen produces lactic acid and causes cellular calcium uptake.

It is in this context that the therapeutic effects of saturated fats, carbon dioxide, progesterone, and thyroid can be understood. They restore stability to a system that has been stimulated beyond its capacity to adapt without injury.

Fatigue, Aging, and Recuperation

Ray Peat's Newsletter, 2013

- Old people and sick people tire easily. Surprisingly, little is known to explain that common fact.
- Myths about lactic acid and oxygen debt have misdirected most fatigue research.
- The cellular processes involved in fatigue overlap with those of aging.
- Knowledge about the mechanisms of fatigue should be useful in preventing some tissue swelling disorders, organ failure, degenerative calcification, and other energy-related problems.

Glossary

- Uncoupling: In cellular respiration, oxidation of "fuel" in the mitochondrion is coupled to the phosphorylation of ADP, forming ATP. Uncouplers are chemicals that allow oxidation to proceed without producing the usual amount of ATP.
- DNP: Dinitrophenol, an uncoupler that was once popular as a weight-loss drug.
- NAD^+ and NADH: Nicotinamide adenine dinucleotide, and its reduced form are coenzymes for many oxidation and reduction reactions in cells.
- Hyperammonemia: The presence of too much ammonia in the blood.
- Vicinal water: water near surfaces, especially hydrophobic surfaces, that is physically and chemically different from ordinary water.
- Hydrophobic: insoluble in water, a nonpolar oil-like molecule that repels water.

UNLIKE the somewhat technical medical concept of "stress," the idea of fatigue is something everyone understands, to some extent. Hans Selye's studies of stress weren't widely accepted until about 40 years after their publication, but some of the main investigators of the

fatigue phenomenon are still practically unknown in the universities, many years after they published their work.

Several things have kept fatigue research from advancing, including the common feeling that fatigue is already sufficiently understood, and that it is somehow trivial, compared to problems such as growth, reproduction, and disease.

Fatigue is usually described as decreased responsiveness resulting from over-exertion: For example, a muscle's decreased strength or speed of contraction, or a nerve's decreased speed of conduction, or a sense organ's decreased ability to detect or to discriminate. Another meaning of fatigue, a decreased resistance or strength, can be applied to materials, as well as to some biological functions, for example when fatigue leads to sickness or infections.

"Responsiveness" implies sensitivity, and decreased sensitivity to stimulation can be seen in fatigued sense organs, nerves, muscles, and many other types of cell—immune cells, secretory cells, etc. Even plant cells have very similar processes of excitability that can be depleted by repetition.

In a series of lectures to the Royal Society in England (1895–1901), the physicist Jagadis Chandra Bose described work that at first excited, and then disturbed, many physicists and biologists. He had invented devices for both producing and detecting electromagnetic waves, and he had been the first to produce millimeter length radio waves (microwaves). In Marconi's first transatlantic radio transmission Bose's signal detecting device was used. This device was based on the fact that two pieces of metal in superficial contact became electrically fused (cohered) in the presence of an electrical or electromagnetic field. After they cohered, a mechanical shock would separate them, breaking the electrical fusion.

When Bose was experimenting with his "self-restoring coherer," a semiconducting device that spontaneously broke the connection without being mechanically shaken, he observed that it became insensitive after prolonged use, that is, it lost its self-restoring capacity, but that after a rest, it recovered its sensitivity. He recognized the complex behavior of his instrument as being very similar to the electrical physiology of living cells.

He then began a series of experiments on plants, animals, and minerals, that showed similar responses to all kinds of stimulation, including mechanical and thermal and electromagnetic.

The idea of metal fatigue wasn't new, but Bose was able to think far beyond the ideas of the metallurgists. Biologists were thinking of electrical responsiveness as a defining feature of life, and Bose demonstrated that plants had electrical responsiveness very similar to that of animals, but also that similar reactions could be demonstrated in minerals.

This was what disturbed the English scientists. Sensitivity, irritability, fatigue, and memory were supposed to be special properties related to life, and maybe to consciousness. For the Englishmen, there were religious implications in this Hindu's research.

There were several reasons that European and American scientists couldn't accept the universal nature of the electrical properties that they were studying in animals. One of their motives was to see life as something immaterial, or of an absolutely different nature than inorganic matter. Another problem had to do with the developing belief that the special properties of life were enclosed in the hereditary substance of each cell, and that the electrical functions of cells were produced entirely by the presence of a membrane, surrounding a drop of water containing randomly moving dissolved chemicals. For the membrane electricity theory, it was essential to believe in the random behavior of things dissolved in the cell water.

So they considered the electrical-mechanical reactions and interactions of minerals to be so unlike the processes of life that it was inappropriate to see analogies between them. Minerals were composed of atoms, and, according to the doctrine of the time, they could have no "physiological" functions except on the atomic scale. It was more than 20 years before mainstream physicists began thinking about "delocalized" forces and fields in minerals.

Between 1915 and 1934, Michael Polanyi made many observations that made it clear that the old kind of electrical atomism was completely unfounded. The behavior of mineral crystals, and the interactions between different phases of material, such as gas or liquid with a solid, could be understood only in terms of relatively long-range forces. Polanyi's experiments showed, for example, that events on the surface of a crystal modified the strength and deformability of the crystal.

Many others between 1900 and 1940— Lepeschkin, Nasonov, Bungenberg de Jong, and Solco Tromp, for example—argued that the sensitivity of protoplasm had to be understood in terms of long range order, something like a liquid crystalline state of matter that would require

some of the kinds of knowledge of matter that were being developed by physicists, metallurgists, and a variety of others investigating the condensed states of matter.

But the mainstream biologists preferred to describe cells in terms that would make impossible any of the responsivities or sensitivities seen in the "simple" solid state of minerals. To defend their ideology of the immateriality of life, they denied that the subtlest features of matter had anything to do with life, reducing life to a debased set of special, merely theoretical, mechanisms. The now defunct physical theory of merely localized atomic electrical forces became the paradigm for the new biology. The many demonstrations of coherent, ordered physical behavior of the cytoplasm, for example Gurwitch's mitogenic radiation, were dismissed with prejudice.

During G. W. Crile's long career (1889–1941), understanding shock, biological energy, and fatigue were his main concerns. He believed that shock was the result of brain exhaustion, and in one of his last publications he showed that the brains from exhausted animals produced less bioluminescence than those from rested animals. His importance was in demonstrating that fatigue and shock are systemic conditions of the organism, rather than isolated events in muscles and nerves. Recent publications are showing the validity of this view. Crile's approach to the prevention and treatment of shock was based on isolating the damaged area with local anesthetics. Blocking the nerves from one injured part of the body, for example the sciatic nerve in the leg, could preserve energy production (and normal cell functions) throughout the rest of the body.

About 30 years earlier (1901), Vvedensky had demonstrated that some types of fatigue appear to be a defensive blocking of responsiveness, such that intense stimulation would produce no response, while weak stimulation could sometimes produce a response. These changes affected cell functions in a variety of ways, that he called narcosis and parabiosis.

There have been two popular ways to "explain" fatigue, one by saying that the cell's energy (usually thought of as ATP or glycogen) is used up, the other saying that the accumulation of a metabolic product (usually lactic acid) prevents further functioning. The obvious problem with these explanations is that the fatigue response is quite independent of those metabolic changes. Another problem is that those ideas don't explain the real changes that occur in cells that are demonstrating fatigue.

Fatigued cells take up water, and become heavier. They also become more permeable, and leak. When more oxygen is made available, they are less resistant to fatigue, and when the organism is made slightly hypoxic, as at high altitude, muscles have more endurance, and are stronger, and nerves conduct more quickly. These facts don't fit with the standard model of the cell, in which its sensitivity is strictly governed by the behavior of its "membrane." (For example, how can a membrane leak large molecules at the same time that it is intact and causing the cell to swell osmotically?) They are consistent with the model of the cell that treats protoplasm as a special phase of matter.

Another feature of fatigue (and often of aging, stress, and sickness) is that the relaxation of muscles is retarded and impaired.

Hypothyroidism causes muscle relaxation to be slowed, both in skeletal muscles and in the heart. F/Z. Meerson showed that stress causes heart muscles to be exposed to increased calcium, followed by breakdown of fats and proteins, and that these changes keep the injured heart in a continuous state of partial contraction, making it stiff, and resistant to complete contractile shortening. When many cardiologists talk about the heart's stiffness, they are thinking of muscular thickening and fibrosis, but those are late consequences of the kind of contractile, unrelaxed stiffness that Meerson described.

The hypothyroid heart does eventually become fibrotic, but before that, it is just unable to relax properly, and unable to contract fully. This failure to empty fully with each contraction is a kind of "heart failure," but it can be corrected very quickly by supplementing thyroid. Even the fibrotic heart can recover under the influence of adequate thyroid.

The analogy of the "coherer" would suggest that the overstimulated muscle isn't able to decohere itself, until it has had a rest. It responds to stimulation, lets the energy flow, but then can't turn it off, and the energy keeps flowing, because of a change in physical state.

Albert Szent-Györgyi was probably the first person to seriously investigate the semiconducting properties of living material. Since he was aware of W. F. Koch's idea of a free radical catalyst to support oxidative metabolism, his suggestion in 1941 that cellular proteins could function as electrical conductors (or semiconductors) was very likely based on his research in cellular respiration, as well as on his work with muscle proteins. He had observed that ATP lowers the viscosity of a solution of the muscle protein myosin, and that it would cause a filament

formed by precipitating myosin to contract. The polymerization and contraction of proteins under the influence of free radicals was at the heart of W. F. Koch's therapeutic ideas, but Koch's work was about 100 years too early, by medical standards.

Szent-Györgyi observed that, although ATP was involved in the contraction of muscles, its post-mortem disappearance caused the contraction and hardening of muscles known as rigor mortis. When he put hardened dead muscles into a solution of ATP, they relaxed and softened. The relaxed state is a state with adequate energy reserves.

After Szent-Györgyi moved to the U.S., in 1947, he demonstrated the effect of muscle cytoplasm on the behavior of fluorescent substances, which was analogous to that of ice, until the muscle was stimulated. During contraction, the fluorescent material behaved as it would in ordinary liquid water. This effect involved the stabilization of the excited state of electrons. This single demonstration should have caused biologists to abandon the membrane theory of cellular excitation, and to return to basic physics for their understanding of cell behavior. The implications of Szent-Györgyi's work were enormous for biology and medicine, and even for the understanding of semiconductors, but most of the world was hypnotized by a simple textbook model of cell membranes.

Szent-Györgyi also demonstrated that the combination of properly balanced electron donors and electron acceptors (D-A pairs) would cause a muscle to contract. He compared this to "doping" an inorganic superconductor, to regulate its electronic behavior. Although these experiments were done half a century after Koch's application of free radical chemistry to medicine, they still didn't rouse the pharmaceutical industry from its toxic slumber.

I suspect that it was Szent-Györgyi's research with those interesting electronic properties of cellular water and proteins that in 1960 gave Linus Pauling the idea to explain anesthesia, specifically noble gas anesthesia, in terms of water clathrate formation, the restructuring of cellular water by the hydrophobic atom or molecule of an anesthetic. His suggestion caused a reaction among biologists that discouraged research into the subject for about 40 years.

Gilbert Ling's view of cytoplasmic structure gives a different emphasis to the function of electrons, which I think is an essential complement to Szent-Györgyi's view. Ling's emphasis is on how the inductive effect of adsorbed substances (for example, ATP and progesterone has powerful

adsorptive effects) on proteins changes the charge concentration on ionizable groups. When the charge concentration is in one configuration (more acidic), the preferred counterion is potassium, and in another (less acidic) configuration, it is sodium.

Gilbert Ling's biophysical calculations were useful to physical chemists, and were soon put to practical use for understanding ion exchange resins, such as water softeners. Many sorts of evidence showed their validity for cell physiology, but nearly all biologists rejected them, preferring to talk about membranes, pumps, and channels, despite the evidence showing that the properties ascribed to those are simply impossible. NMR imaging (MRI) was developed by Raymond Damadian specifically as an application of Ling's description of cell physiology.

Although metals are conductors, the function of the coherers of Bose and others shows that the surface is a semiconductor, that requires the slight excitation of an electromagnetic wave to become conductive, at which point the conduction band of electrons in the metal becomes coherent and extends from one particle into the others. The surface of any phase of a substance has electronic properties distinct from those of the bulk phase, and in a sense the interface constitutes a special phase of matter. When the electrons of the interface lose their special properties, the structure of the whole system changes.

When a muscle cell is stimulated enough to cause a contraction, the interruption of its resting phase causes a shift in the charge concentration on the proteins, potassium ions are exchanged for sodium ions, calcium ions enter, and phosphate ions separate from ATP, and are replaced by the transfer of phosphate to ADP from creatine phosphate.

Since the quantum physicist E. Schroedinger wrote his book, Time's Arrow, people have often thought of life in terms of negentropy, going against the general tendency of entropy to increase, except for aging and death, which are seen as obeying a law of increasing entropy. But A. Zotin investigated organisms, rather than abstractions about electrons, and shows that aging involves a decrease in entropy, and a slowing of metabolism. The decrease of entropy with aging, according to his view, would be analogous to crystallization, a sort of progressive freezing.

When a nerve is stimulated, it releases energy suddenly, and much of this heat seems to be the result of a change of structure in the cytoplasm, since (in crustaceans' nerves, which can function at low temperature) during the resting recovery of the nerve, its temperature goes slightly

below the ambient temperature, despite the release of some heat from the chemical changes of metabolism, stimulated by the nerve's activity.

When a physical change is endothermic, as the nerve's recovery is, that can be interpreted as an increase in overall entropy, as when a rubber band spontaneously contracts, and becomes cooler.

Bose's rested coherer, which, with time, spontaneously recovered its semiconductive (i.e., relatively insulating) property, wasn't being powered by metabolism. As the particles returned to their relatively isolated state, there was a decrease of order, and the change was probably somewhat like the spontaneous energy change in the stimulated crustacean nerve. I assume the change would result from the absorption of environmental heat, possibly with infrared resonance with electron conduction bands.

Seeing the structure of the cytoplasm as something like a spring-driven mechanism, able to bounce between two states or "phases," makes it easier to see cellular fatigue as something different from the various metabolic energy sources, ATP, glycogen, and oxygen, which—contrary to conventional assumptions—aren't closely tied to the functional losses occurring in fatigue.

The role of metabolism, then, becomes analogous to the role of the "tapper" in the early forms of the coherer.

Water in its normal state is a dielectric. But when it is polarized by an electrical charge, or by the presence of a phase boundary, its normal state is altered. This is the special interfacial water, or vicinal water. With the movement of ions (mainly potassium, sodium, calcium, and magnesium) during excitation, the state of the cellular water is necessarily changed by the presence of different substances. In the excited state, cell water is less hydrophobic, more hydrophilic than in the relaxed state. A network of "hydrophobic" interactions extends through the relaxed cell. One of the properties of a dielectric is that it tends to move into the space between charges, with a force similar in principle to that involved in dielectrophoresis.

In the resting state, potassium is the main inorganic ion, and it is associated with acidic groups, such as aspartic and glutamic acid. During excitation, potassium is partly exchanged for sodium, which becomes the preferred counter-ion for the acid groups, and calcium enters the cell along with the sodium. Potassium's interaction with water is very weak (its hydration has been called negative), allowing water

to form the structures that are stable in the presence of hydrophobic surfaces. Sodium and especially calcium (smaller atoms, with higher surface charge concentration) powerfully interact with water molecules, more strongly than water interacts with itself, disrupting the delicate somewhat hydrophobic structures of the intracellular water.

(Calcium, with its two charges, has important binding and stabilizing functions in the resting cell. In the excited cell, these internal calcium ions are released, while extracellular calcium ions enter the cell.)

With the increased movement of charged particles during the stimulation of a nerve or muscle, as one kind of counterion is exchanged for another, and the destruction of some of the water's structure, there are more opportunities for bulk dielectric water to enter cells, interfering with the arrangement of proteins, and tending to cause swelling and separation of the structural elements of the cell. Electron micrographs of fatigued muscle show a remarkable separation of the actin and myosin proteins.

In the excited state, NMR studies show that cell water behaves more like bulk water, that is, its molecular movements are relatively free, indicating the momentary loss of the interfacial state. In this state, the uptake of water, and the fatigue-related swelling of nerves and muscles, would be driven at least partly by the principle that a dielectric tends to be pulled into the spaces separating charges. The bulk water that enters a cell during the breakdown of vicinal water functions as an extraneous material somewhat beyond the cell's control.

These bulk-like high dielectric properties of water in the excited cellular state can explain many changes of enzyme activity. Previously nonpolar lipids would develop a negative surface charge,[1] which would tend to increase their oxidation and degradation. With the loss of the interfacial water, the cell's high energy resting state is replaced by an active mobilization of its resources, to maintain and restore the cell's structure. Metabolic energy begins to flow into the processes of restoration, serving the function of the tapper in the earliest coherers.

Looking at fatigability, muscle contraction, and nerve conduction in a variety of situations, we can test some of the traditional explanations, and see how well the newer "bioelectronic" explanations fits the facts. Osmotic pressure, hydrostatic pressure, atmospheric pressure, and the degree of metabolic stimulation by thyroid hormone affect fatigue in ways that aren't consistent with the membrane-electrical doctrine.

The production of lactic acid during intense muscle activity led some people to suggest that fatigue occurred when the muscle wasn't getting enough oxygen, but experiments show that fatigue sets in while adequate oxygen is being delivered to the muscle. Underwater divers sometimes get an excess of oxygen, and that often causes muscle fatigue and soreness. At high altitudes, where there is relatively little oxygen, strength and endurance can increase.

An excess of oxygen can slow nerve conduction, while hypoxia can accelerate it. (Increasing the delivery of oxygen at higher pressure doesn't increase the cellular use of oxygen or decrease lactic acid production in the exercising muscle,[2] but it will increase lipid peroxidation.)

High hydrostatic pressure causes muscles to contract, though for many years the membrane-doctrinaires couldn't accept that. Underwater divers experience brain excitation under very high pressure. Since vicinal water has a larger volume than ordinary water (analogous to the expansion when ice is formed, though the volume increase in cell water is slightly less, about 4%, than in ice, which is 11% more voluminous than liquid water), compression under high pressure converts vicinal cell water to the state that occurs in the excited cell, the way ice melts under pressure. The excited state exists as long as water remains in that state.

These changes of state under pressure are reminiscent of Bose's use of pressure in some of his coherers, and of the fact that pressure alters the sensitivity of electrons in a semiconductor, by altering their "band gap," the amount of energy needed to make them enter the conductive zone.

One of the early demonstrations that cell water undergoes a phase change during muscle contraction involved simply measuring the volume of an isolated muscle. With stimulation and contraction, the volume of the muscle decreases slightly. (The muscle was immersed in water in a sealed chamber, and the volume decrease in the whole chamber was measured.) This corresponds to the conversion of vicinal water to bulk-like (dielectric) water. (The threatening implications of those experiments with spontaneous volume change were very annoying to many biologists of my professors' generation.)

In the stimulated state, the cell's uptake of water from its environment coincides closely with its electrical and thermal activity, and its expulsion of water coincides with its recovery. In a small nerve fiber,

or near the surface of a larger fiber, these changes are very fast, and in a large muscle the uptake of water is faster than the flow of water from capillaries can match, but it will become massive if stimulation is continued for several minutes. For example, two minutes of stimulation can cause a muscle's overall weight to increase by 6 %, but its extracellular compartment loses 4 %, so the muscle cells gain much more than 6 % of their weight in that short time.[3] The water that is taken up by cells is taken from the blood, which becomes relatively dehydrated and thicker in the process.

The belief in "semipermeable membranes" (which hasn't been a viable explanation of cell physiology for a very long time) forces people to explain cell swelling osmotically, which means that they simply assume that the number of solute particles inside the cell has drastically increased in a very short time. In Tasaki's experiments (1980, 1981, 1982), the swelling in a nerve coincides with the electrical action potential, which, according to the osmotic explanation, means that a very large increase in internal osmolarity happened in essentially no time. The action potential comes and goes in about 2 ms. The swelling also coincides with heat production and shortening of the nerve fiber. The shrinkage of the nerve fiber after the end of the action potential may be just as rapid, and the membrane theory offers no explanation for that, either. (But the restoration of the unswollen state can be very prolonged, depending on conditions extrinsic to the particular muscle or cell.) Troshin's survey of the theory of osmotic regulation of cell volume showed that the idea of the cell as a membrane osmometer was false, but very few biologists read his book.

Since the excited or fatigued muscle or nerve swells and gains weight, it's interesting to see what happens to their sensitivity and strength when they are exposed to hypotonic solutions that tend to promote swelling, or to hypertonic solutions, that help to prevent swelling.

In a hypotonic solution, cells are excited (Lang, et al., 1995: "Exposure of aortic strips from guinea-pigs to hypotonic extracellular fluid is followed by marked vasoconstriction…"), but the early excitation is followed by decreased responsiveness (Ohba, et al., 1984: "Exposure of muscle to hypotonic solutions (70 % of normal solution) produced initially a transient increase in twitch after which twitch declined below the control level"). Hypertonic solutions tend to produce relaxation in normal muscles, including the aorta,[4] but when muscle function is

impaired (especially in the circulatory system, as in shock) they improve contractile function (Elgjo, et al., 1998: "The maximum contraction force measured in isolated right papillary muscles *ex vivo* was significantly greater in HSD-treated than normal saline-treated animals"). Athletes can lose 4% of their weight by dehydration without decreasing their muscular strength.

Hypothyroidism tends to cause loss of sodium from the blood, and the hyponatremia sometimes leads to a generalized hypotonicity of the body fluids. The thyroid hormone itself functions as an antioxidant, but much of its protective effect against cell damage is probably the result of preventing cell swelling and accelerating the removal of calcium from the cell. (Swelling, like fatigue, causes intracellular calcium to increase.)

The electrical surface charging of lipids in bulk water probably accounts for the increased lipid peroxidation that occurs in fatigue, edema, and hypothyroidism, when water loses its normal partial hydrophobicity. Increased carbon dioxide is known to decrease lipid peroxidation, and its production requires adequate thyroid function.

Thyroid stimulation of oxygen consumption tends to prevent lactic acid production, because it keeps the cytoplasm in a state of relative oxidation, i.e., it keeps the concentration of NAD^+ hundreds of times higher than that of NADH. NADH is required for the conversion of pyruvate to lactate. It is also the source of reducing potential in many kinds of toxic redox cycling, that generate lipid peroxides, and it maintains the sulfhydryl system, involving the balance of reduced glutathione with the sulfhydryl-disulfide system of protein bonds, which governs the cell's electronic state and affects its balance of hydrophobicity and hydrophilicity.

The harmful lipid oxidation interferes with energy production and regulatory processes, and is responsible for some of the prolonged effects of fatigue, swelling, and hypothyroidism. These lingering effects of lipid oxidation are undoubtedly amplified by the presence of larger amounts of unstable polyunsaturated fats, as the energy demands of the fatigued state mobilize free fatty acids from the tissues.

One of the oldest tests for hypothyroidism was the Achilles tendon reflex test, in which the rate of relaxation of the calf muscle corresponded to thyroid function—the relaxation is slow in hypothyroid people. Water, sodium and calcium are more slowly expelled by the hypothyroid muscle. Exactly the same slow relaxation occurs in the hypothyroid heart muscle,

contributing to congestive heart failure, because the semi-contracted heart can't receive as much blood as the normally relaxed heart. The hypothyroid blood vessels are unable to relax properly, contributing to hypertension. Hypothyroid nerves don't easily return to their energized relaxed state, leading to insomnia, paresthesias, movement disorders, and nerves that are swollen and very susceptible to pressure damage.

With aging, hypothyroidism, stress, and fatigue, the amount of estrogen in the body typically rises. Estrogen is catabolic for muscle, and causes systemic edema, and nerve excitation. It weakens muscle contraction in the bladder, although it lowers the threshold for stimulation of sensation and contraction.[5] This is the pattern that causes people to wake up frequently, to pass a small amount of urine. (Progesterone has the opposite effect in the urinary bladder, raising the threshold of response, but strengthening contraction, as it does in the gallbladder.) Estrogen lowers stimulation threshold in the gallbladder, as it does in the brain. Part of its excitatory action might be the result of increased hypotonic tissue water, but its effects on nerve thresholds are practically instantaneous.

In 1971 and '72, I gave some of the reasons for thinking that estrogen's biological effects result from its direct effects on cell water, causing it to become more like bulk (high dielectric) water. For example, NMR (spin echo) of estrogen treated uterus and of the uterus from an old animal were closer to bulk water than that of a young animal. Estrogen, like fatigue or excessive oxygen, slows nerve conduction.

Lactic acid production increases with fatigue, aging, hypothyroidism, estrogen excess, and other inefficient biological states. Its presence, when oxygen is available, indicates that something is interfering with efficient oxidative energy metabolism. Ammonia, free fatty acids, and various inflammatory cytokines are also likely to increase in those stress states.

A dangerously high level of ammonia in the blood (hyperammonemia) can be produced by exhaustive exercise, but also by hyperbaric oxygen (or a high concentration of oxygen), by high estrogen, and by hypothyroidism. It tends to be associated with an excess of lactic acid, probably because ammonia stimulates glycolysis. Excess oxygen, like hypothyroidism, is equivalent to "hyperventilation," in producing an abnormally low level of carbon dioxide in the blood. The Krebs cycle, during stress, is limited by the unavailability of carbon dioxide. These

factors result in the waste of glucose, turning it into lactic acid, rather than carbon dioxide and energy. In these ways, the metabolism of fatigued muscle (or any cell under stress) is similar to tumor metabolism.

Hyperammonemia disturbs excitatory processes, and can cause seizures, as well as stupor, and is probably involved in mania and depression. Lithium happens to complex electronically with ammonia, and I think that accounts for some of its therapeutic effects, but carbon dioxide is the main physiological factor in the elimination of ammonia, since it combines with it to form urea. The changes in cell water in the excited/fatigued state represent an increase in the water's "structural temperature," and that would imply that less carbon dioxide could remain dissolved during excitation.

Eating sugar and using caffeine, which increases the oxidation of sugar,[6] can reduce fatigue, both subjectively and objectively. Metabolically, they increase the production of carbon dioxide. Increasing sugar decreases the liberation and use of fatty acids, and by a variety of mechanisms, helps to lower the production of ammonia, lactate, and inflammatory cytokines. (Lactic acid, in combination with acidosis and free phospholipids, can interfere with efficient cell functions.[7,8]) Free fatty acids release tryptophan from albumin, contributing to the formation of serotonin, which increases the sense of fatigue.

Aspirin and niacin help to prevent fatigue symptoms, and to prevent many of the harmful systemic oxidative after-effects. (Both are antilipolytic; aspirin uncouples mitochondria.)

Uncoupling of mitochondrial oxidative metabolism from ATP production helps to consume the sugar which otherwise would be diverted into lactic acid, and converts it into carbon dioxide instead. Mild hypoxia, as at high altitude, suppresses lactic acid production ("the lactate paradox"), and increases the amount of carbon dioxide in tissues.

Aspirin and thyroid (T_3) increase uncoupling. A drug that used to be used for weight reduction, DNP, also uncouples mitochondrial metabolism, and, surprisingly, it has some of the beneficial effects of thyroid and aspirin. It stimulates the consumption of lactic acid and the formation of carbon dioxide.

The squirrel monkey, which on average weighs about 2 or 3 pounds as an adult, lives much longer than other mammals of its size, usually about 20 years, as long as 27. It has an extremely high rate of oxygen consumption. This is probably the result of natural uncoupling of the

mitochondria, similar to that seen in long-lived mice. Mice with 17 % higher resting oxygen consumption lived 36 % longer than slow respiring mice of a related strain.[9]

Living at a high altitude, people tend to eat more and stay leaner than when they live near sea level. Apparently, their mitochondria are relatively uncoupled, and they have more mitochondria, which would partly account for their lower production of lactic acid during muscular exertion. Increased thyroid activity, too, tends to increase mitochondrial mass, as well as their uncoupling.

Most of the things that we think of as fatigue result from disturbances of the hydration of cells, whose sensitivity, composition, and structure change according to the extent of the disturbance. The hydration is governed by the cells' "electrical" properties, which are regulated by internal metabolic processes and by systemic processes. When cellular fatigue reaches a certain point, only the interactions of all the organs can restore stable cellular structure and functions. The liver eliminates lactic acid and ammonia, the adrenals and gonads provide stabilizing steroids, and the brain alters activity and behavior, in ways that can reverse most of the effects of fatigue.

But, when the tissues contain large amounts of polyunsaturated fats, every episode of fatigue and prolonged excitation leaves a residue of oxidative damage, and the adaptive mechanisms become progressively less effective. When the most powerful adaptive mechanisms, such as the timely synthesis of progesterone, pregnenolone, DHEA, T_3, and the inhibitory transmitters, GABA and glycine, fail, then some of the primitive defense mechanisms will become chronically activated, and even sleep may fail to restore normal cellular water and metabolism. Hyperventilation often becomes a problem, making capillary leakiness worse.

Water in the body occupies three major compartments—blood vessels, extracellular matrix, and the moist cell substance itself—and its condition in each compartment is a little different, and subject to variation. There are no textbooks in use in the U.S. that treat intracellular water scientifically, and the result is that physicians are confused when they see patients with edema or with disturbances in blood volume. It rarely occurs to physicians to consider disturbances of water distribution in problems such as chronic fatigue, fibromyalgia, sleep disturbances, frequent urination, slow bladder emptying, anxiety, paresthesia, movement

disorders, the tunnel syndromes, or even slowed thinking, but "intracellular fatigue" leading to over-hydration is probably the central problem in these, and many other degenerative and inflammatory problems.

The improvements in cell functions and water distribution that are inversely related to oxygen pressure, and directly related to carbon dioxide, won't be discussed in medical textbooks until they have given up the idea of membrane-regulated cells.

The "treatment" for intracellular fatigue consists of normalizing thyroid and steroid metabolism, and eating a diet including fruit juice, milk, some eggs or liver, and gelatin, assuring adequate calcium, potassium sodium, and magnesium, and using supplements of niacin-amide, aspirin, and carbon dioxide when necessary. Simply increasing carbon dioxide decreases lactic acid and ammonia, increases GABA (the sleep improving nerve inhibitor), and regulates mineral and water disposition.

One of the outcomes of the study of the physiology of fatigue is that it leads to a better understanding of cells in general, and offers some new insights into aging, inflammation, and a variety of stress-related diseases.

Fats, Functions & Malfunctions

Ray Peat's Newsletter, 2013

AROUND the beginning of the 20th century, it was commonly believed that aging resulted from the accumulation of insoluble metabolic by-products, sort of like the clinker ash in a coal furnace. Later, age pigment or lipofuscin, was proposed to be such a material. It is a brown pigment that generally increases with age, and its formation is increased by consumption of unsaturated fats, by vitamin E deficiency, by stress, and by exposure to excess estrogen. Although the pigment can contribute to the degenerative processes, aging involves much more than the accumulation of insoluble debris; aging increases the tendency to form the debris, as well as vice versa.

There is a growing recognition that a persistent increase of free fatty acids in the serum, which is seen in shock, heart failure, and aging, indicates a bad prognosis, but there is no generally recognized explanation for the fact that free fatty acids are harmful. I want to mention some evidence showing that it is the accumulation of polyunsaturated fats in the body that makes them harmful.

The physical and functional properties of saturated fatty acids and polyunsaturated fatty acids (PUFA) are as different from each other as day is from night. The different fatty acids are directly involved, very often with opposite effects, in cell division and growth, cell stability and dissolution, the organization of cells, tissues, and organs, the regulation of pituitary hormones, adrenalin and sympathetic nervous activation, histamine and serotonin synthesis, adrenal cortex hormones, thyroid hormones, testosterone, estrogen, activators of the immune system and inflammation (cytokines), autoimmune diseases, detoxification, obesity, diabetes, puberty, epilepsy,

Saturated fatty acids terminate the stress reactions, polyunsaturated fatty acids amplify them.

The most highly unsaturated fats, including DHA, accumulate with aging, and their toxic fragments are increased in Alzheimer's disease.

The most highly unsaturated fats found in fish oil break down into chemicals that block the use of glucose and oxygen.

The ratio of saturated fatty acids to polyunsaturated fatty acids is decreased in cancer.

Omega-3 fats promote metastasis.

Parkinson's disease, other degenerative nerve diseases and Alzheimer's disease, cancer, heart failure, atherosclerosis, and strokes. In each of these situations, the PUFA have harmful effects.

Most people are surprised to hear about the systematically harmful effects of the common dietary polyunsaturated fats and the protective effects of saturated fats. That's because there is a pervasive mythology of fats in our culture. Officials are proposing to tax saturated fats. Laws are being passed prescribing the fats that can be served in restaurants, and people write letters to editors about them, and great amounts of money are spent publicizing the importance of eating the right fats. Their focus is on obesity, atherosclerosis, and heart disease. The details of the myth change a little, as new fat products and industries appear.

As I understand the basic myth, the difference between the "essential" polyunsaturated fats and the saturated fats has to do with their shape—the unsaturated fatty acids bend or fold in a way that makes them more mobile than saturated fats of the same length, and this causes the all-important "membranes" of cells to be more fluid, and thus to have "better functions," though the myth isn't very clear on the issue of fluidity and functionality. At that point, it passes responsibility to the more fundamental biological myth, of the metabolically active cell membrane.

Practically everyone learns, in grade school and from television, about the good and the bad oils, and cell membranes, but it might seem likely that people who spend their lives investigating the role of fats in organisms would have acquired a different, more complicated, view. But one of the most famous food fat researchers, J.M. Bourre, has succinctly (and thoughtlessly) expressed his understanding of the function of fatty substances in the body: "In fact the brain, after adipose tissue, is the organ richest in lipids, whose only role is to participate in membrane structure."[1] The fact that his editor let him publish the statement shows how the myth functions, causing people to accept things because they are "common knowledge." The influence of the medical and pharmaceutical industries is so pervasive that it becomes the context for most biological research.

Luckily, many people are working outside the myth, in specialized problems of physiology and cell biology, and their observations are showing a reality much more complex and interesting than the mythology.

When we eat more protein or carbohydrate than we need, the excess can be converted to fats, to be stored (as triglycerides), but even on a

maintenance diet we synthesize some fats that are essential parts of all of our cells, including a great variety of phospholipids. People seldom talk about the importance of fats in the nucleus of the cell, but every nucleus contains a variety of lipids—phospholipids, sphingolipids, cholesterol, even triglycerides—similar to those that are found elsewhere in the cell and in every part of the body, including the brain.[2,3] Phospholipids are often considered to be "membrane lipids," but they have been demonstrated in association with elements of the cell's skeleton, involved in cell division, rather than in membranes.[4]

The cytoskeleton, a fibrous framework of the cell that's responsible for maintaining the organized structure of the cell, internal movement of organelles, coordination, locomotion, and cell division, is made up of three main kinds of protein, and all of these are affected differently by different kinds of fat.

Actions of lipids on the cell skeleton can change cells' movements, migrations, and invasiveness. Unsaturated fats cause clumping of some types of cell filament, condensation and polymerization of other types, in ways that are associated with brain degenerative diseases and cancer. For example, DHA alters the structure of the protein alpha-synuclein, causing it to take the form seen in Parkinson's disease and other brain conditions. The synucleins regulate various structural proteins, and are affected by stress, aging, and estrogen exposure, as well as by the polyunsaturated fats. One type of synuclein is involved in the promotion of breast cancer. Saturated fatty acids have exactly the opposite effects of PUFA on the synucleins, reversing the polymerization caused by the PUFA.[5]

When cancers are metastasizing, their phospholipids contain less stearic acid than the less malignant tumors,[6] patients with advanced cancer had less stearic acid in their red blood cells,[7] and adding stearic acid to their food delayed the development of cancer in mice.[8] The degree of saturation of the body's fatty acids corresponds to resistance to several types of cancer that have been studied.[9,10]

The phospholipids are being discussed in relation to drugs that can modify "signaling" by acting on phospholipid receptors, using language that was developed in relation to hormones. A surface barrier membrane, with receptors that send signals to the nucleus, is invoked by many of the recent discussions of phospholipids. There's no question that the fats do affect regulatory processes, but the theory and the language should

correspond to the physiological and ecological realities. Vernadski's metaphor, that an organism is a "whirlwind of atoms," is probably more appropriate than "targeted signals and receptors" for understanding the physiology of fatty acids and phospholipids. The rate of change and renewal of these structural fats is very high. In rats, one study found a 30 % decrease in the total phospholipid pool in the brain in the first 30 minutes after death.[11]

Another study in the brains of living rats found that a particular class of brain lipids, ethanolamine plasmalogens, had a turnover time of about 5 h.[12] (This type of lipid is an important component of the lipoproteins secreted by the liver into the serum,[13] and is also a major lipid in the heart and brain.) Stresses such as the loss of sleep cause great distortions in phospholipid metabolism throughout the body, especially in the brain and liver.

Actions of lipids on the cell skeleton can change cells' movements, migrations, and invasiveness, even in short term experiments. The effects of the "essential fatty acid" linoleic acid have been compared to the drug colchicine, which is known to interfere with the cell skeleton and cell division. According to Hoover, et al.,[14] it disturbed the structure of the cytoskeleton more than colchicine does; it caused the cell filaments to clump together, while saturated fatty acids didn't have such an effect.

The fatty molecules that participate in the normal cell functions are made by cells even when they are grown in a fat-free solution in a culture dish. They include saturated fatty acids such as palmitate and stearate, and omega-9 unsaturated fats, such as oleic acid and omega-9 polyunsaturated fatty acids. The saturated fatty acids found in the nucleus associated with the chromosomes are resistant to change when the composition of the animal's diet changes,[15] while the unsaturated fats change according to the diet. These intracellular fats are essential for cell division and the regulation of the genes, and for cell survival.[3] Although cells make the saturated fats that participate in those basic functions, the high rate of metabolism means that some of the lipids will quickly reflect in their structure the free fatty acids that circulate in the blood. The fats in the blood reflect the individual's diet history, but recently eaten fats can appear in the serum as free fatty acids, if the liver isn't able to convert them into triglycerides.

The polyunsaturated fatty acids differ from the saturated fats in many ways, besides their shape and their melting temperature, and each type of

fatty acid is unique in its combination of properties. The polyunsaturated fatty acids, made by plants (in the case of fish oils, they are made by algae), are less stable than the saturated fats, and the omega-3 and omega-6 fats derived from them, are very susceptible to breaking down into toxins, especially in warm-blooded animals. Other differences between saturated and polyunsaturated fats are in their effects on surfaces (as surfactant), charges (dielectric effects), acidity, and their solubility in water relative to their solubility in oil. The polyunsaturated fatty acids are many times more water soluble than saturated fatty acids of the same length. This property probably explains why only palmitic acid functions as a surfactant in the lungs, allowing the air sacs to stay open, while unsaturated fats cause lung edema and respiratory failure.

The great difference in water/oil solubility affects the strength of binding between a fatty acid and the lipophilic, oil-like, parts of proteins. When a protein has a region with a high affinity for lipids that contain double bonds, polyunsaturated fatty acids will displace saturated fats, and they can sometimes displace hormones containing multiple double bonds, such as thyroxine and estrogen, from the proteins that have a high specificity for those hormones. Transthyretin (also called prealbumin) is important as a carrier of the thyroid hormone and vitamin A. The unsaturation of vitamin A and of thyroxin allow them to bind firmly with transthyretin and certain other proteins, but the unsaturated fatty acids are able to displace them, with an efficiency that increases with the number of double bonds, from linoleic (with two double bonds) through DHA (with six double bonds).

The large amount of albumin in the blood is important in normal fatty acid binding and transport, but it is also an important part of our detoxifying system, since it can carry absorbed toxins from the intestine, lungs, or skin to the liver, for detoxification. Albumin facilitates the uptake of saturated fatty acids by cells of various types,[16] and its ability to bind fatty acids can protect cells to some extent from the unsaturated fatty acids.[17] The liver's detoxification system processes some polyunsaturated fats for excretion, along with hormones and environmental toxins.

The movement of proteins from the plasma into cells has often been denied, but there is clear evidence that a variety of proteins, including IgG, transferrin haptoglobin, and albumin can be found in a variety of cells, even in the brain.[18] Cells are lipophilic, and absorb molecules in

proportion to their fattiness; this long ago led people to theorize that cells are coated with a fat membrane.

The idea of a semipermeable membrane, similar in function to the membrane inside an eggshell, was proposed about 150 years ago, to explain the ability of living cells to concentrate certain chemicals, such as potassium ions, while excluding others, such as sodium ions. This idea of a molecular sieve was shown to be invalid when radioactive isotopes made it possible to observe that sodium ions diffuse freely into cells, and it was replaced by the idea of a metabolically active membrane, containing "pumps" that made up for the inability to exclude various things, and that allowed cells to retain high concentrations of some dissolved substances that are free to diffuse out of the cell. The general idea of the membrane as a barrier persisted as a sort of "common sense" idea, that has made people ignore experiments that show that some large molecules, including some proteins, can quickly and massively enter cells. Albumin and transthyretin are two proteins that are sometimes found in large quantities inside cells, and their primary importance is that they bind and transport biologically active oily molecules.

While the competition by PUFA for protein binding sites blocks the effects of thyroid hormone and vitamin A, the action of PUFA on the sex steroid binding protein (SBP, or SSBG, for sex steroid binding globulin) increases the activity of estrogen. That's because the SSBG neutralizes estrogen by binding it, keeping it out of cells; free PUFA keep it from binding estrogen.[19] People with low SSBG/estrogen ratio have an increased risk of cancer. When the SSBG protein is free of estrogen, it is able to enter cells, and in that estrogen-free state it probably serves a similar protective function, capturing estrogen molecules that enter cells before they can act on other proteins or chromosomes. Transthyretin, the main transporter of thyroid and vitamin A, and albumin (which can also transport thyroid hormone) are both able to enter cells, while loaded with thyroid hormone and vitamin A. Albumin becomes more lipophilic as it binds more lipid molecules, so its tendency to enter cells increases in proportion to its fat burden. Albumin in the urine is a problem associated with diabetes and kidney disease; albumin loaded with fatty acids passes from the blood into the urine more easily than unloaded albumin, and it is the fatty acids, not the albumin, which causes the kidney damage.[20] It's possible that SSBG's opposite behavior, entering cells only when it

carries no hormones, is the result of becoming less lipophilic when it's loaded with estrogen.

Since most people believe that cells are enclosed within a barrier membrane, a new industry has appeared to sell special products to "target" or "deliver" proteins into cells across the barrier. Combining anything with fat makes it more likely to enter cells. Stress (which increases free fatty acids and lowers cell energy) makes cells more permeable, admitting a broader range of substances, including those that are less lipophilic.

Linoleic acid and arachidonic acid, which are said to "make the lipid membrane more permeable," in fact make the whole cell more permeable, by binding to the structural proteins throughout the cell, increasing their affinity for water, causing generalized swelling, as well as mitochondrial swelling (leading to reduced oxidative function or disintegration), allowing more calcium to enter the cell, activating excitatory processes, stimulating a redox shift away from oxidation and toward inflammation, leading to either (inappropriate) growth or death of the cell.

When we don't eat for many hours, our glycogen stores decrease, and adrenaline secretion is increased, liberating more glucose as long as glycogen is available, but also liberating fatty acids from the fatty tissues. When the diet has chronically contained more polyunsaturated fats than can be oxidized immediately or detoxified by the liver, the fat stores will contain a disproportionate amount of them, since fat cells preferentially oxidize saturated fats for their own energy, and the greater water solubility of the PUFA causes them to be preferentially released into the bloodstream during stress.

In good health, especially in children, the stress hormones are produced only in the amount needed, because of negative feedback from the free saturated fatty acids, which inhibit the production of adrenalin and adrenal steroids, and eating protein and carbohydrate will quickly end the stress. But when the fat stores contain mainly PUFA, the free fatty acids in the serum will be mostly linoleic acid and arachidonic acid, and smaller amounts of other unsaturated fatty acids. These PUFA stimulate the stress hormones, ACTH, cortisol, adrenaline, glucagon, and prolactin, which increase lipolysis, producing more fatty acids in a vicious circle. In the relative absence of PUFA, the stress reaction is self

limiting, but under the influence of PUFA, the stress response becomes self-amplifying.

When stress is very intense, as in trauma or sepsis, the reaction of liberating fatty acids can become dangerously counter-productive, producing the state of shock. In shock, the liberation of free fatty acids interferes with the use of glucose for energy and causes cells to take up water and calcium (depleting blood volume and reducing circulation) and to leak ATP, enzymes, and other cell contents,[21–24] in something like a systemic inflammatory state[25] often leading to death.

The remarkable resistance of "essential fatty acid deficient" animals to shock[26–28] shows that the polyunsaturated fats are centrally involved in the maladaptive reactions of shock. The cellular changes that occur in shock—calcium retention, leakiness, reduced energy production—are seen in aging and the degenerative diseases; the stress hormones and free fatty acids tend to be chronically higher in old age, and an outstanding feature of old age is the reduced ability to tolerate stress and to recover from injuries.

Despite the instability of polyunsaturated fatty acids, which tend to break down into toxic fragments, and despite their tendency to be preferentially liberated from fat cells during stress, the proportion of them in many tissues increases with age.[29–34] This progressive increase with age can be seen already in early childhood.[35] The reason for this increase seems to be that the saturated fatty acids are preferentially oxidized by many types of cell, (fat cells can slowly oxidize fat for their own energy maintenance). Albumin preferentially delivers saturated fatty acids into actively metabolizing cells such at the heart[16] for use as fuel. This preferential oxidation would explain Hans Selye's results, in which canola oil in the diet caused the death of heart cells, but when the animals received stearic acid in addition to the canola oil, their hearts showed no sign of damage.

Since healthy cells are very lipophilic, saturated fatty acids would have a greater tendency to enter them than the more water soluble polyunsaturated fats, especially those with 4, 5, or 6 double bonds, but as cells become chronically stressed they more easily admit the unsaturated fats, which slow oxidative metabolism and create free radical damage. The free radicals are an effect of stress and aging, as well as a factor in its progression.

When stress signals activate enzymes in fat cells to release free fatty acids from the stored triglycerides, the enzymes in the cytoplasm act on the surface of the droplet of fat. This means that the fatty acids with the greatest water solubility will be liberated from the fat to move into the blood stream, while the more oil soluble fatty acids will remain in the droplet. The long chain of saturated carbon atoms (8 in the case of oleic acid, 15 in palmitic acid, and 17 in stearic acid) in the "tail" of oleic, palmitic, and stearic acid will be buried in the fat droplet, while the tail of the n-3 fatty acids, with only 2 saturated carbons, will be the most exposed to the lipolytic enzymes. This means that the n-3 fatty acids are the first to be liberated during stress, the n-6 fatty acids next. Saturated and monounsaturated fatty acids are selectively retained by fat cells.[36]

Women are known to have a greater susceptibility than men to lipolysis, with higher levels of free fatty acids in the serum and liver, because of the effects of estrogen and related hormones.

Women on average have more DHA circulating in the serum than men.[37–39] This highly unsaturated fatty acid is the first to be liberated from the fat stores under stress, and, biologically, the meaning of estrogen is to mimic stress. Estrogen and polyunsaturated fatty acids have similar actions on cells, increasing their water content and calcium uptake. Long before the Women's Health Initiative reported in 2002 that the use of estrogen increased the risk of dementia, it was known that the incidence of Alzhemer's disease was 2 or 3 times higher in women than in men. Men with Alzheimer's disease have higher levels of estrogen than normal men.[40] The amount of DHA in the brain (and other tissues) increases with aging, and its breakdown products, including neuroprostanes, are associated with dementia. Higher levels of DHA and total PUFA are found in the plasma of demented patients.[41]

Another interesting association of the highly unsaturated fats and estrogen in relation to brain function is that DHA increases the entry of estrogen into the pregnant uterus, but inhibits the entry of progesterone,[42] which is crucial for brain cell growth. When Dirix, et al.,[43] supplemented pregnant women with PUFA, they found that fetal memory was impaired.

The crucial mitochondrial respiratory enzyme, cytochrome c oxidase, declines with aging,[44] as the lipid cardiolipin declines, and the enzyme's activity can be restored to the level of young animals by adding cardiolipin. The composition of cardiolipin changes with aging, "specifically

an increase in highly unsaturated fatty acids".[45] Other lipids, such as a phosphatidylcholine containing two myristic acid groups, can support the enzyme's activity.[46] Even supplementing old animals with hydrogenated peanut oil restores mitochondrial respiration to about 80 % of normal.[47]

Supplementing thyroid hormone increases mitochondrial cardiolipin.[48] Eliminating the polyunsaturated fats from the diet increases mitochondrial respiration.[49]

Excitotoxicity is the process in which activation of a nerve cell beyond its capacity to produce energy injures or kills the cell, by increasing intracellular calcium. Glutamic acid and aspartic acid are the normal neurotransmitter excitatory amino acids. Estrogen increases the activity of the excitatory transmitter glutamate,[50] and glutamate increases the release of free fatty acids.[51] DHA (more strongly even than arachidonic acid) inhibits the uptake of the excitotoxic amino acid aspartate, and in some situations glutamate, prolonging their actions. Thymocytes are much more easily killed by stress than nerve cells, and they are easy to study. The PUFA kill them by increasing their intracellular calcium. The toxicity of DHA is greater than that of EPA, whose toxicity is greater than alpha-linolenic acid, and linoleic acid was the most potent.[52] Excitotoxicity is probably an important factor in Alzheimer's disease.[53]

When the brain is injured, DHA and arachidonic acid contribute to brain edema, weakening the blood-brain-barrier, increasing protein breakdown, inflammation, and peroxidation, while a similar amount of stearic acid in the same situation caused no harm.[54] In other situations, such as the important intestinal barrier, EPA and DHA also greatly increased the permeability.[55]

The process by which excitotoxicity kills a cell is probably a foreshortened version of the aging process.

Excitotoxins (including endotoxin) increase the formation of neuroprostanes and isoprostanes (from n-3 and n-6 PUFA),[56] and acrolein and other fragments, which inhibit the use of glucose and oxygen. DHA and EPA produce acrolein and HHE, which react with lysine groups in proteins, and modify nucleic acids, changing the bases in DNA.

Increased intracellular calcium activates lipolysis (by phospholipases), producing more free fatty acids, as well as excitation and protein breakdown, and in the brain neurodegenerative diseases, calcium excess contributes to the clumping of synuclein,[57] an important regulator of

the cytoskeletal proteins. The reduced function of normal synuclein makes cells more susceptible to excitotoxicity.[58]

If the cells adapt to the increased calcium, rather than dying, their sensitivity is reduced. This is probably involved in the "defensive inhibition" seen in many types of cell. In the brain, DHA and arachidonic acid "brought the cells to a new steady state of a moderately elevated (intracellular calcium) level, where the cells became virtually insensitive to external stimuli. This new steady state can be considered as a mechanism of self-protection."[59] In the heart, the PUFAs decreased the sensitivity to stimulation[60] and conduction velocity.[61,62] Both DHA and EPA inhibit calcium-ATPase (which keeps intracellular calcium low to allow normal neurotransmission) in the cerebral cortex; this suggests "a mechanism that explains the dampening effect of omega-3 fatty acids on neuronal activity".[63]

In normal aging, most processes are slowed, including nerve conduction velocity, and conduction velocity in the heart.[64] A similar "dampening" or desensitization is seen in sensory, endocrine, and immune systems, as well as in energy metabolism. Calorie restriction, by decreasing the age-related accumulation of PUFA (20:4, 22:4, and 22:5), can prevent the decrease of sensitivity, for example in lymphoid cells.[29] The known effects of the unsaturated fats on the organizational framework of the cell are consistent with the changes that occur in aging.

One of the essential protective functions that decline with aging is the liver's ability to detoxify chemicals, by combining them with glucuronic acid, making them water soluble so that they can be excreted in the urine. The liver (and also the intestine and stomach) efficiently process DHA by glucuronidation.[65] Oleic acid, one of the fats that we synthesize ourselves, increases (about 8-fold) the activity of the glucuronidation process.[66,67] However, this system is inhibited by the PUFA, arachidonic acid,[68] and also by linoleic acid,[69] in one of the processes that contribute to the accumulation of PUFA with aging.

Animals that naturally have a relatively low level of the highly unsaturated fats in their tissues have the greatest longevity. For example, the naked mole rate has a life expectancy of more than 28 years, about 9 times as long as other rodents of a similar size. Only about 2 % to 6 % of its phospholipids contain DHA, while about 27 % to 57 % of the phospholipids of mice contain DHA.[70]

The famously long-lived people of Azerbaijan eat a diet containing a low ratio of unsaturated to saturated fats, emphasizing fruits, vegetables, and dairy products.[71]

Some of the clearest evidence of the protective effects of saturated fats has been published by A.A. Nanji's group, showing that they can reverse the inflammation, necrosis, and fibrosis of alcoholic liver disease, even with continued alcohol consumption, while fish oil and other unsaturated fats exacerbate the problem.[72] Glycine protects against fat accumulation in alcohol-induced liver injury,[73] suggesting that dietary gelatin would complement the protective effects of saturated fats.

The least stable n-3 fats which accumulate with age and gradually reduce energy production also have their short term effects on endurance. Endurance was much lower in rats fed a high n-3 fat diet, and the effect persisted even after 6 weeks on a standard diet.[74] Analogous, but less extreme effects are seen even in salmon, which showed increased oxidative stress on a high n-3 diet (DHA or EPA), and lower mitochondrial cytochrome oxidase activity.[75]

Maintaining a high rate of oxidative metabolism, without calorie restriction, retards the accumulation of PUFA, and a high metabolic rate is associated with longevity. An adequate amount of sugar maintains both a high rate of metabolism, and a high respiratory quotient, i.e., high production of carbon dioxide. Mole rats, bats, and queen bees, with an unusually great longevity, are chronically exposed to high levels of carbon dioxide. Carbon dioxide forms carbamino bonds with the amino groups of proteins, inhibiting their reaction with the reactive "glycating" fragments of PUFA.

To minimize the accumulation of the highly unsaturated fatty acids with aging, it's probably reasonable to reduce the amount of them directly consumed in foods, such as fish, but since they are made in our own tissues from the "essential fatty acids," linoleic and linolenic acids, it's more important to minimize the consumption of those (from plants, pork, and poultry, for example).

In the resting state, muscles consume mainly fats, so maintaining relatively large muscles is important for preventing the accumulation of fats.

Fats and Degeneration

Ray Peat's Newsletter, 2009

WHEN a person uses a drug, there is generally an awareness that the benefit has to be weighed against the side effects. But if something is treated as a "nutrient," especially an "essential nutrient," there is an implication that it won't produce undesirable side effects.

Over the last thirty years I have asked several prominent oil researchers what the evidence is that there is such a thing as an "essential fatty acid." One professor cited a single publication about a solitary sick person who recovered from some sickness after being given some unsaturated fat. (If he had known of any better evidence, wouldn't he have mentioned it?) The others (if they answered at all) cited "Burr and Burr, 1929.[1]" The surprising thing about that answer is that these people can consider any nutritional research from 1929 to be definitive. It's very much like quoting a 1929 opinion of a physicist regarding the procedure for making a hydrogen bomb. What was known about nutrition in 1929? Most of the B vitamins weren't even suspected, and it had been only two or three years since "vitamin B" had been subdivided into two factors,

50 years ago, in the first phase of marketing the polyunsaturated fatty acids (PUFA), linoleic acid was "heart protective," and the saturated fats raised cholesterol and caused heart disease.

In the second phase, the other "essential fatty acid," linolenic acid, was said to be even better than linoleic acid.

In the third phase, the longer chain omega-3 (omega minus three, or n minus three) fatty acids, DHA and EPA, are said to be even better than linolenic acid.

Along the way, the highly unsaturated arachidonic acid, which we and other animals make out of the linoleic acid in foods, was coming to be identified with the "harmful animal fats." But we just didn't hear much about how the amount of arachidonic acid in the tissues depended on the amount of linoleic acid in the diet.

U.S. marketing dominates the world economy, including of course the communication media, so we shouldn't expect to hear much about the role of PUFA in causing cancer, diabetes, obesity, aging, thrombosis, arthritis and immunodeficiency, or to hear about the benefits of the saturated fats.

The saturated fats include the "tropical fats," because they are synthesized in very warm organisms, and are very stable at those temperatures. Their stability offers some protection against the unstable PUFA.

Several of the degenerative conditions produced by the "essential fatty acids" can be reversed by use of saturated fats, varying in length from the short chains of coconut oil to the very long chains of waxes.

the "antineuritic factor," B_1, and the "growth factor," B_2. Burr had no way of really understanding what deficiencies or toxicities were present in his experimental diet.

A few years after the first experiments, Burr put one of his "essential fatty acid deficient" rats under a bell jar to measure its metabolic rate, and found that the deficient animals were metabolizing 50 % faster than rats that were given linoleic and linolenic acids as part of their diet. That was an important observation, but Burr didn't understand its implications. Later, many experiments showed that the polyunsaturated fats slowed metabolism by profoundly interfering with the function of the thyroid hormone and the cellular respiratory apparatus. Without the toxic fats, respiratory energy metabolism was very intense, and a diet that was nutritionally sufficient for a sluggish animal wouldn't necessarily be adequate for the vigorous animals.

Several publications between 1936 and 1944 made it very clear that Burr's basic animal diet was deficient in various nutrients, especially vitamin B_6. The disease that appeared in Burr's animals could be cured by fat free B-vitamin preparations, or by purified vitamin B_6 when it became available. A zinc deficiency produces similar symptoms, and at the time Burr did his experiments, there was no information on the effects of fats on mineral absorption. If a diet is barely adequate in the essential minerals, increasing the metabolic rate, or decreasing intestinal absorption of minerals, will produce mineral deficiencies and metabolic problems.

Although "Burr's disease" clearly turned out to be a B-vitamin deficiency, probably combined with a mineral deficiency, it continues to be cited as the basis justifying the multibillion dollar industry that has grown up around the "essential" oils.

Two years before Burr's experiment, German researchers found that a fat-free diet prevented almost all spontaneous cancers in rats. Later work showed that the polyunsaturated fats both initiate and promote cancer. With that knowledge, the people who kept claiming that "linoleic, linolenic, and maybe arachidonic acid are the essential fatty acids," should have devoted some effort to finding out how much of that "essential nutrient" was enough, so that people could minimize their consumption of the carcinogenic stuff.

Between the first and second world wars, cod liver oil was recommended as a vitamin supplement, at first as a source of vitamin A, and

later as a source of vitamins A and D. But in the late 1940s, experimenters used it as the main fat in dogs' diet, and found that they all died from cancer, while the dogs on a standard diet had only a 5 % cancer mortality. That sort of information, and the availability of synthetic vitamins, led to the decreased use of cod liver oil.

But around that time, the seed oil industry was in crisis because the use of those oils in paints and plastics was being displaced by new compounds made from petroleum. The industry needed new markets, and discovered ways to convince the public that seed oils were better than animal fats. They were called the "heart protective oils," though human studies soon showed the same results that the animal studies had, namely, that they were toxic to the heart and increased the incidence of cancer.

The "lipid hypothesis" of heart disease argued that cholesterol in the blood caused atherosclerosis, and that the polyunsaturated oils lowered the amount of cholesterol in the blood. Leaving behind the concept of nutritional essentiality, this allowed the industry (and their academic supporters, such as Frederick Stare at Harvard) to begin promoting the oils as having drug-like therapeutic properties. Larger amounts of polyunsaturated fat were supposed to be more protective by lowering the cholesterol, and were to be substituted for the saturated fats, which supposedly raised cholesterol and increased heart disease, producing atherosclerotic plaques in the blood vessels and increasing the formation of blood clots.

Since all ordinary foods contain significant amounts of the polyunsaturated fats, there was no reason to think that, even if they were essential nutrients, people were likely to become deficient in them. So the idea of treating the seed oils as drug-like substances, to be taken in large amounts, appealed to the food oil industry.

Prostaglandins, which are produced in the body by oxidizing the polyunsaturated fatty acids, provided an opportunity for the drug industry to get involved in a new market, and the prostaglandins offered a new way of arguing for the nutritional essentiality of linoleic and related acids: A whole system of "hormones" is made from these molecules. Since some of the prostaglandins suppress immunity, cause inflammation and promote cancer growth, some people have divided them into the "good prostaglandins" and the "bad prostaglandins."

PGI_2, or prostacyclin, is considered to be a good prostaglandin, because it causes vasodilatation, and so drug companies have made their own synthetic equivalents: Epoprostenol, iloprost, taprostene, ciprostene, UT-15, beraprost, and cicaprost. Some of these are being investigated for possible use in killing cancer.

But many very useful drugs that already existed, including cortisol and aspirin, were found to achieve some of their most important effects by inhibiting the formation of the prostaglandins. It was the body's load of polyunsaturated fats which made it very susceptible to inflammation, stress, trauma, infection, radiation, hormone imbalance, and other fundamental problems, and drugs like aspirin and cortisone, which limit the activation of the stored "essential fatty acids," gain their remarkable range of beneficial effects partly by the restraint they impose on those stored toxins.

Increasingly, the liberation of arachidonic acid from tissues during stress is seen as a central factor in all forms of stress, either acute (as in burns or exercise) or chronic (as in diabetes or aging). And, as the fat stores become more toxic, it seems that they more readily liberate the free fatty acids.[2]

During this same period, a few experimenters were finding that animals which were fed a diet lacking the "essential" fatty acids had some remarkable properties: They consumed oxygen and calories at a very high rate, their mitochondria were unusually tough and stable, their tissues could be transplanted into other animals without provoking immunological rejection, and they were very hard to kill by trauma and a wide variety of toxins that easily provoke lethal shock in animals on the usual diet. As the Germans had seen in 1927, they had a low susceptibility to cancer, and new studies were showing that they weren't susceptible to various fibrotic conditions, including alcoholic liver cirrhosis.

In 1967 a major nutrition publication, *Present Knowledge in Nutrition*, published Hartroft and Porta's observation that the "age pigment," lipofuscin, was formed in proportion to the amount of polyunsaturated fat and oxidants in the diet. The new interest in organ transplantation led to the discovery that the polyunsaturated fats prolonged graft survival, by suppressing the immune system. Immunosuppression was considered to have a role in the carcinogenicity of the "essential" fatty acids.

Around the same time, there were studies that showed that unsaturated fats retarded brain development and produced obesity.

Substances very much like the prostaglandins, called isoprostanes and neuroprostanes, are formed spontaneously from highly unsaturated fatty acids, and are useful as indicators of the rate of lipid peroxidation in the body. Most of the products of lipid peroxidation are toxic, as a result of their reactions with proteins, DNA, and the mitochondria. The age-related glycation products that are usually blamed on sugar, are largely the result of peroxidation of the polyunsaturated fatty acids.

Through the 1970s, this sort of information about the harmful effects of the PUFA was being slowly assimilated by the culture, though many dietitians still spoke of "the essential fatty acids, vitamin F." By 1980, it looked as though responsible researchers would see the promotion of cancer, heart disease, mitochondrial damage, hypothyroidism and immunosuppression caused by the polyunsaturated fats as their most important feature, and would see that there had never been a basis for believing that they were essential nutrients.

But then, without acknowledging that there had been a problem with the doctrine of essentiality, fat researchers just started changing the subject, shifting the public discourse to safer, more profitable topics. The fats that had been called essential, but that had so many toxic effects, were no longer emphasized, and the failed idea of "essentiality" was shifted to different categories of polyunsaturated fats.

The addition of the long chain highly unsaturated fats to baby food formulas was recently approved, on the basis of their supposed "essentiality for brain development." One of the newer arguments for the essentiality of the PUFA is that "they are needed for making cell membranes." But human cells can grow and divide in artificial culture solutions which contain none of the polyunsaturated fats, and no one has claimed that they are growing "without membranes."

The long chain fats found in fish and some algae don't interfere with animal enzymes as strongly as the seed oils do, and so by comparison, they aren't so harmful. They are also so unstable that relatively little of them is stored in the tissues. (And when they are used as food additives, it's necessary to use antioxidants to keep them from becoming smelly and acutely toxic.)

When meat is grilled at a high temperature, the normally spaced double bonds in PUFA migrate towards each other, becoming more stable, so that linoleic acid is turned into "conjugated linoleic acid." This analog of the "essential" linoleic acid competes against the linoleic acid

in tissues, and protects against cancer, atherosclerosis, inflammation and other effects of the normal PUFA. Presumably, anything which interferes with the essential fatty acids is protective, when the organism contains dangerous amounts of PUFA. Even the trans-isomers of the unsaturated fatty acids (found in butterfat, and convertible into conjugated linoleic acid) can be protective against cancer.

In the 1980s the oil promoters were becoming more sophisticated, and were publishing many experiments in which the fish oils were compared with corn oil, or safflower, or soy oil, and in many of those experiments, the animals' health was better when they didn't eat the very toxic seed oils, that contained the "essential fatty acids," linoleic and linolenic acids.

Besides comparing the fish oils to the stronger toxins, another trick is to take advantage of the same immunosuppressive property that had seemed troublesome, and to emphasize their ability to temporarily alleviate some autoimmune or allergic diseases. X-rays were once used that way, to treat arthritis and ringworm, for example.

And, knowing that cancer cells have the ability to consume large amounts of fatty acids, they would test these fats in tissue culture dishes, and demonstrate that they were poisonous, cytotoxic, to the fast growing cancer cells. Although they caused cancer in animals, if they could be shown to kill cancer cells in a dish, they could be sold as anticancer drugs/nutrients, with the special mystique of being "essential fatty acids." Strangely, their ability to kill cancer cells under some circumstances and to suppress some immunological reactions is being promoted in close association with the doctrine that these fats are nutritionally essential.

Arachidonic acid is made from linoleic acid, and so those two oils were considered as roughly equivalent in their ability to meet our nutritional needs, but a large part of current research is devoted to showing the details of how fish oils protect against arachidonic acid. The "balance" between the omega-3 and the omega-6 fatty acids is increasingly being presented as a defense against the toxic omega-6 fats. But the accumulation of unsaturated fats with aging makes any defense increasingly difficult, and the extreme instability of the highly unsaturated omega-3 fats creates additional problems.

PUFA and x-rays have many biological effects in common. They are immunosuppressive, but they produce their own inflammatory reactions, starting with increased permeability of capillaries, disturbed coagulation

and proteolysis, and producing fibrosis and tumefaction or tissue atrophy. This isn't just a coincidence, since ionizing radiation attacks the highly unstable polyunsaturated molecules, simply accelerating processes that ordinarily happen more slowly as a result of stress and aging.

Prolonged stress eventually tends to be a self-sustaining process, impairing the efficient respiratory production of energy, converting muscle tissue to amino acids, suppressing the thyroid, and activating further mobilization of fatty acids. Fatty acids are mobilized from within the structure of cells by phospholipases, and from fat tissues by other lipases.

The highly unsaturated fatty acids, as well as the ordinary "essential fatty acids," act directly to increase capillary permeability, even without conversion into prostaglandins, and they interfere in many ways with the clotting and clot removal systems. The effects of PUFA taken in a meal probably disturb the clotting system more than the same quantity of saturated fat, contrary to many of the older publications. The PUFA are widely believed to prevent clotting, but when cod liver oil is given to "EFA deficient" animals, it activates the formation of clots.[3] An opposite effect is seen when a long chain fatty acid synergizes with aspirin, to restrain clotting.[4]

Fibrosis is a generalized consequence of the abnormal capillary permeability produced by things that disrupt the clotting system. Estrogen, with its known contribution to the formation of blood clots and edema and fibrosis and tumors, achieves part of its effect by maintaining a chronically high level of free fatty acids, preferentially liberating arachidonic acid, rather than saturated fatty acids.

Butter, beef fat, and lamb fat are the only mostly saturated fats produced on a large scale in the U.S., and the cheapness/profitability of the seed oils made it easy to displace them. But, in the face of the immense amount of propagandistic "health" claims that have been made against the saturated fats, it's instructive to look at some of their actual effects, especially on the clotting system, and the related fibrotic reactions.

The saturated fatty acids are very unreactive chemically. Coconut oil, despite containing about 1 % of the unstable PUFA, can be left in a bucket at room temperature for a year or more without showing any evidence of deterioration, suggesting that the predominance of saturated fat acts as an antioxidant for the unsaturated molecules. In the body, the

saturated fats seem to act the same way, preventing or even reversing many of the conditions caused by oxidation of fats.

The stress-induced liberation of arachidonic acid causes blood vessels to leak, and this allows fibrin to escape from the blood stream, into the basement membrane and beyond into the extracellular matrix, where it produces fibrosis. (Cancer, autoimmune diseases, and heart disease involve the same inflammatory, thrombotic, fibrotic processes as the nominal fibroses.) Scleroderma, liver cirrhosis, fibrosis of the lungs, heart, and other organs, and all the diseases in which fibrous tissue becomes dense and progressively contracts, involve similar processes, and the treatments which are successful are those that stop the inflammation produced by the oxidation of the polyunsaturated fatty acids.

Retroperitoneal fibrosis is now known to be produced by estrogen, and is treated by antiestrogenic and antiserotonergic drugs, but as early as 1940 Alejandro Lipschutz demonstrated that chronic exposure to very low doses of estrogen produced fibromas in essentially every part of the body. Earlier, Loeb had studied the action of large doses of estrogen, which produced fibrosis of the uterus, as if it had accelerated aging. Following Lipschutz' work, in which he demonstrated the "antifibromatogenic" actions of pregnenolone and progesterone, several Argentine researchers showed that progesterone prevented and cured abdominal adhesions and other fibrotic conditions, including retroperitoneal fibrosis.

Since estrogen produces both leakiness of the capillaries and excessive formation of fibrin, its effects will be seen first in the organs where it concentrates, but eventually anywhere capillaries leak fibrin. Estrogen activates the phospholipase which liberates arachidonic acid, and progesterone inhibits that phospholipase.

As the fat tissues become more burdened with arachidonic acid, they release it more easily in response to moderately lipolytic stress signals. This could explain the increased levels of free fatty acids and lipid peroxidation that occur with aging. In animals that are "deficient" in the polyunsaturated fatty acids, adrenalin doesn't have the lipolytic effect that it does in animals on the standard diet. With aging, there is not only a tendency to have chronically higher free fatty acids in the blood, but for those fatty acids to be more unsaturated. The phospholipids of mitochondria and microsomes become more unsaturated with aging.[5,6]

In the human retina there is a similar accumulation of PUFA with aging,[7] which implies that the aged retina will be more easily damaged by light.

Several studies suggest that a high degree of unsaturation in the fats is fundamentally related to the aging process, since long lived species have a lower degree of unsaturation in their fats. Caloric restriction decreases the age-related accumulation of the fatty acids with 4 and 5 double bonds.

Although publicity has emphasized the anti-inflammatory effects of fish oil, experiments show that it is extremely effective in producing alcohol-related liver cirrhosis. Breakdown products of polyunsaturated fats (isoprostanes and 4-HNE) are found in the blood of people with alcoholic liver disease.[8] In the absence of polyunsaturated fats, alcohol doesn't produce cirrhosis. Saturated fats allow the fibrosis to regress:

"A diet enriched in saturated fatty acids effectively reverses alcohol-induced necrosis, inflammation, and fibrosis despite continued alcohol consumption. The therapeutic effects of saturated fatty acids may be explained, at least in part, by reduced endotoxemia and lipid peroxidation…"[9,10]

In these studies, the animals were switched from fish oil to either palm oil or medium chain triglycerides (a major fraction of coconut oil). In other studies,[11] show that fibrinogen, in "a clotting-like process," is involved in the development of liver fibrosis, and that this appears to provide a basis for the growth of additional extracellular matrix.

Brown, et al.,[12] discussed this developmental process (leaky capillaries, fibrosis) in relation to wound healing, lung disease, and tumor growth.

The relatively few studies of fish oil and linoleic acid that compare them with palmitic acid or coconut oil have produced some very important results. For example, pigs exposed to endotoxin developed severe lung problems (resembling "shock lung") when they had been on a diet with either fish oil or Intralipid (which is mostly linoleic acid, used for intravenous feeding in hospitals), but not after palmitic acid.[13]

Eating low-fat seafood (sole, whitefish, turbot, scallops, oysters, lobster, shrimp, squid, etc.) once in a while can provide useful trace minerals, without much risk. However, fish from some parts of the ocean contain industrial contaminants in the fat, and large fish such as tuna, swordfish, Chilean sea bass and halibut contain toxic amounts of

mercury in the muscles. Chilean sea bass (Patagonian toothfish) is very high in fat, too.

About ten years ago I met a young man with a degenerative brain disease, and was interested in the fact that he (working on a fishing boat) had been eating almost a pound of salmon per day for several years. There is now enough information regarding the neurotoxic effects of fish oil to justify avoidance of the fatty fish.

Some of the current advertising is promoting fish oil to prevent cancer, so it's important to remember that there are many studies showing that it increases cancer.

The developmental and physiological significance of the type of fatty acid in the diet has been established for a long time, but cultural stereotypes and commercial interests are threatened by it, so it can't be discussed publicly.

Food-Junk and Some Mystery Ailments

Fatigue, Alzheimer's, Colitis, Immunodeficiency

Ray Peat's Newsletter, 2005

YEARS ago, I noticed that Oregon was one of the few states that still had real whipping cream and cottage cheese without additives, so I have been trustingly using cream in my coffee every day. Last week, I noticed that my cream listed carrageenan in its ingredients. Over the years, I have avoided carrageenan-containing foods such as apple cider, hot dogs, most ice creams and prepared sauces and jellies, because they caused me to have serious allergic symptoms. Carrageenan has been found to cause colitis and anaphylaxis in humans, but it is often present in baby "formulas" and a wide range of milk products, with the result that many people have come to believe that it was the milk-product that was responsible for their allergic symptoms. Because the regulators claim that it is a safe natural substance, it is very likely that it sometimes appears in foods that don't list it on the label, for example when it is part of another ingredient.

In the 1940s, carrageenan, a polysaccharide made from a type of seaweed, was recognized as a dangerous allergen. Since then it has become a standard laboratory material to use to produce inflammatory tumors (granulomas), immunodeficiency, arthritis, and other inflammations. It has also become an increasingly common material in the food industry. Articles are often written to praise its usefulness and to claim that it doesn't produce cancer in healthy animals. Its presence in food, like that of the polyester imitation fat, microcrystalline cellulose, and many other polymers used to stabilize emulsions or to increase smoothness, is often justified by the doctrine that these molecules are too large to be absorbed. There are two points that are deliberately ignored by the food-safety regulators, 1) these materials can interact dangerously with intestinal bacteria, and 2) they can be absorbed, in the process called "persorption."

The sulfites (sodium bisulfite, potassium metabisulfite, etc.) have been used as preservatives in foods and drugs for a long time, even though they were known to cause intense allergic reactions in some people. Fresh vegetables and fish, dried fruits, ham and other preserved meats, hominy, pickles, canned vegetables and juices, and wines were

commonly treated with large amounts of the sulfites to prevent darkening and the development of unpleasant odors. People with asthma were known to be more sensitive than other people, but the sulfites could cause a fatal asthma-like attack even in someone who had never had asthma. Even when this was known, drugs used to treat asthma were preserved with sulfites. Was the information just slow to reach the people who made the products? No, the manufacturers knew about the deadly nature of their products, but they kept on selling them. The FDA didn't answer letters on the subject, and medical magazines such as J.A.M.A. declined to publish even brief letters seriously discussing the issue. Obviously, since many people died from what the drug companies called "paradoxical bronchoconstriction" when they used the products, the drug companies had to be protected from lawsuits, and the medical magazines and the government regulators did that through the control of information.

I think a similar situation exists now in relation to the effects of carrageenan.

Stress and anxiety sharply reduce the circulation of blood to the intestine and liver. Prolonged stress damages the ability of the intestinal cells to exclude large molecules. Local irritation and inflammation of the intestine also increase its permeability and decrease its ability to exclude harmful materials. But even the normal intestine is able to permit the passage of large molecules and particles, in many cases particles larger than the cells that line the intestine; this persorption of particles has been demonstrated using particles of plastic, starch grains which are sometimes several times larger than blood cells, and many other materials, including carrageenan. One of the reasons it has been easy to convince the public that persorption doesn't happen is that there is a powerful myth in our culture about the existence of a "semipermeable" "plasma membrane" on cells through which only certain specific substances may pass.

About 30 years ago some biologists made a movie of living cells under the microscope, showing an ameboid cell entering another cell, swimming around, and leaving, without encountering any perceptible resistance; persorption of food particles, moving in one side of a cell and out the other, wouldn't seem so mysterious if more people had seen films of that sort.

Also in the 1960s, Gerhard Volkheimer rediscovered the phenomenon of persorption, which had been demonstrated a century earlier. Starch grains, or other hard particles, can be found in the blood, urine, and other fluids after they have been ingested. The iodine stain for starch, and the characteristic shape of the granules, makes their observation very easy. The absorption of immunologically intact proteins and other particles has been demonstrated many times, but myth is more important than fact; all of my biology professors, for example, denied that proteins could be absorbed by any part of the digestive system.

The accepted description of the absorption of chylomicrons, tiny particles of fat, helps to understand the way medical professors think about the intestine. These particles, they say, are disassembled by the intestine cells on one side, their molecular parts are taken up by the cells, and similar particles are excreted out the other side of the cells, into the lymphatic vessels. As they visualize one of these cells, it consists of at least four barriers, with each theoretical cell surface membrane consisting of an outer water-compatible phase, in intramembranal lipid region, and an inner water-compatible phase where the membrane rests on the "cell contents." Endocytosis, for example the ingestion of a bacterial particle by a phagocyte, is described in a similar way, to avoid any breach in the "lipid bilayer membrane."

This mental armature has made it essentially impossible for the biomedical culture to assimilate the facts of persorption, which would have led 150 years ago to the scientific study of allergy and immunology in relation to the digestive system.

Volkheimer found that mice fed raw starch aged at an abnormally fast rate, and when he dissected the starch-fed mice, he found a multitude of starch-grain-blocked arterioles in every organ, each of which caused the death of the cells that depended on the blood supplied by that arteriole. It isn't hard to see how this would affect the functions of organs such as the brain and heart, even without considering the immunological and other implications of the presence of foreign particles randomly distributed through the tissue.

In 1979 some of my students in Mexico wanted a project to do in the lab. Since several traditional foods are made with corn that has been boiled in alkali, I thought it would be valuable to see whether this treatment reduced the ability of the starch grains to be persorbed. For breakfast one day, they ate only atole, tamales, and tortillas, all made

from the alkali treated corn. None of the students could find any starch grains after centrifuging their blood and urine. That led me to substitute those foods whenever possible for other starches.

I have written previously about some of the environmental factors, including radiation, estrogens, and unsaturated fats, that are known to damage the immune system and the brain, and that we have been increasingly exposed to since 1940.

To better understand the nature of the diseases that are now becoming so common, we can look at them in a series, from the bowel, to the liver, to the immune system, and to the brain and hormones.

The incidence of several inflammatory diseases, for example Crohn's disease, a chronic inflammation of the intestine, has been increasing during the last 50 years in the industrialized countries, and at the same time, the incidence of several liver diseases has also been increasing.

The entry of bacteria into the blood stream, which can lead to septicemia, is ordinarily considered to be of importance only in extreme immunodeficiency states, such as old age or in premature infants, but the death rate of young adults from septicemia has been increasing rapidly since the 1940s.

The permeability of the intestine that allows bacteria to enter the blood stream is very serious if the phagocytic cells are weakened. Carrageenan poisoning is one known cause of the disappearance of macrophages. Its powerful immunosuppression would tend to be superimposed onto the immunological damage that has been produced by radiation, unsaturated fats, and estrogens.

The liver tumor that is characteristic of young women using the oral contraceptive pill is a hepatocellular adenoma, which is considered to be a premalignant tumor. In Japan, Mexico, and several European countries, the incidence of hepatocellular tumors has increased steadily and tremendously in recent decades, and it has increased in men as well as in women. This is the sort of tumor that very likely represents an increased burden of toxins absorbed from the bowel. Carrageenan contributes to the disappearance of the liver enzymes (the cytochrome P-450 system) that detoxify drugs, hormones, and a variety of other chemicals.

Carrageenan enters even the intact, uninflamed gut, and damages both chemical defenses and immunological defenses. When it has produced inflammatory bowel damage, the amount absorbed will be

greater, as will the absorption of bacterial endotoxin. Carrageenan and endotoxin synergize in many ways, including their effects on nitric oxide, prostaglandins, toxic free radicals, and the defensive enzyme systems.

The continuing efficient production of energy is a basic aspect of metabolic defense, and this is interrupted by carrageenan and endotoxin. The energy failure becomes part of a vicious circle, in which permeability of the intestine is increased by the very factors that it should exclude.

Once the protective barrier-functions of the intestine and liver have been damaged, allergens and many materials with specific biological effects can enter the tissues. The polysaccharide components of connective tissue constitute a major part of our regulatory system for maintaining differentiated cell functioning, and absorbed starches act as "false signals," with a great capacity for deranging cellular functioning. Several types of research indicate that carrageenan changes cellular function in complex ways, imitating changes seen in cancer, for example.

R.J.V. Pulvertaft found "a close similarity between Burkitt cells and human lymphocytes stimulated by bean extract." He concluded that "…the possibility of a relation between Burkitt's lymphoma and a diet of beans should not be neglected," though he emphasized that other factors must be considered, since most people who eat beans don't develop the disease. The intestinal parasites which are common in tropical Africa can cause inflammation of the bowel, leading to the absorption of large amounts of antigens.

Since the bowel becomes inflamed in influenza, it is reasonable to think that some of the symptoms of "the flu" are produced by absorbed bowel toxins.

The variations in the post-influenza syndromes are very likely influenced by the nature of the bacteria or foods which are present, chronically or at the time of an uncompensated stress or inflammatory disease. K.M. Stevens has argued that while rheumatic fever and glomerulonephritis are caused by the antigens of streptococci, systemic lupus erythematosis (SLE) is probably caused by the antigens of gram-positive lactobacilli found in the normal flora.

Migraine, SLE, chronic fatigue syndrome, thyroid problems, and some kinds of porphyria seem to be more common in women of reproductive age, and are often exacerbated by premenstrual hormone changes. According to Stevens, "SLE is almost entirely a disease of women of child-bearing age. One possibility for this selection could be

that women during this period harbour a peculiar flora. This is indeed the case; large numbers of gram-positive lactobacilli are present in the vagina only during the thirty-odd years when regular menstrual activity is present."

In 1974, I noticed that I consistently got a migraine headache after drinking a lactobacillus milk product, and stopped using (and recommending) yogurt and other lactobacillus foods, though I suspected it was the lactic acid which caused the immediate symptoms. Lactic acid is a metabolic burden, especially when combined with an estrogen excess, but Stevens' main point, about the significance of our immunological response to systemic bacterial antigens, deserves more attention.

On a typical diet, tissues progressively accumulate linoleic acid, and this alters the structure of mitochondrial cardiolipin, which governs the response of the mitochondrial enzymes to the thyroid hormone. This process is especially evident in the female liver. In the "autoimmune" diseases, such as lupus, there are typically antibodies to cardiolipin, as if the body were trying to reject its own tissues, which have been altered by the storage of linoleic acid. The altered mitochondrial function, which is involved in so many symptoms, can become part of a vicious circle, with endotoxin and estrogen having central roles, once the stage has been set by the combination of diet, stress, and toxins.

A few months ago I had a questionnaire circulated in a "fibromyositis" discussion group on the internet, and the consistency of responses was interesting.

The questions were:

1) Have you noticed that any of your symptoms are worse premenstrually?

2) Have you noticed that any symptom is less severe premenstrually?

3) Do any symptoms seem to be worse periodically, but without being associated with the premenstrual time?

4) Did your symptoms appear after use of oral contraceptives or IUD?

Except for one woman who was taking oral contraceptives at the time she became sick, and kept taking them, and who didn't notice any cycle, all of the answers to the first three questions (15 of the 16 who responded) were identical: 1) yes, 2) no, 3) no.

The premenstrual estrogen-dominance usually leads progressively to higher prolactin and lower thyroid function. Estrogen is closely associated with endotoxinemia, and with histamine and nitric oxide formation, and with the whole range of inflammatory and "autoimmune" diseases. Anything that irritates the bowel, leading to increased endotoxin absorption, contributes to the same cluster of metabolic consequences.

I have previously discussed the use of antibiotics (and/or carrot fiber and/or charcoal) to relieve the premenstrual syndrome, and have mentioned the study in which the lifespan was extended by occasionally adding charcoal to the diet. A few years ago, I heard about a Mexican farmer who collected his neighbors' runt pigs, and got them to grow normally by adding charcoal to their diet. This probably achieves the same thing as adding antibiotics to their food, which is practiced by pig farmers in the U.S. to promote growth and efficient use of food. Charcoal, besides binding and removing toxins, is also a powerful catalyst for the oxidative destruction of many toxic chemicals. In a sense, it anticipates the action of the protective enzymes of the intestinal wall and the liver.

Some women with premenstrual fatigue have found that the "premenstrual" phase tends to get longer and longer, until they have chronic fatigue. I found that to be one of the easiest "PMS" problems to correct. When people are older, and have been sick longer, the fatigue problem is likely to involve more systems of the body. The larger the quantity of "toxic fat" stored in the body, the more careful the person must be about increasing metabolic and physical activity. Using more vitamin E, short-chain saturated fats, and other anti-lipid-peroxidation agents is important.

The inflammatory diseases that develop after prolonged stress are sometimes hard to correct. But avoiding exposure to the major toxic allergens—such as carrageenan—is an essential consideration, just as important as correcting the thyroid function and avoiding the antithyroid substances.

Low cholesterol is very commonly involved in the diseases of stress, and—like inadequate dietary protein—will make the system less responsive to supplementary thyroid hormone.

The proliferative aspects of the inflammatory diseases represent, I think, a primitive form of regeneration. Arthritis, atherosclerosis, various granulomatous processes, breast diseases, liver adenomas, etc., provide an opportunity for investigating the various systems and sub-

stances that guide cell proliferation toward reconstruction, rather than obstructive and deformative, degenerative, processes. Degenerative diseases probably all contain clues for understanding regeneration, as I have suggested in relation to Alzheimer's disease and inflammation. I will be talking about these in other newsletters, but the first step will always be to minimize exposure to the disruptive substances.

Gelatin, Stress, Longevity

Ray Peat's Newsletter, 2009

I usually think about something for a long time before I get around to integrating it into my life, sometimes because old habits have to be changed, but usually because our social organization is set up to do things in conventional ways. Our foods reflect our social organization, enforced by laws and rules. When I first went to Mexico to study, many traditional foods were still available even in the city—fried pig skin, served crisp or boiled with a sauce, blood tacos, cartilaginous parts of various animals, chicken-foot soup, crustaceans, insects, etc. Later, when I studied biochemistry, I realized that each part of an organism has a characteristic chemistry and special nutritional value. I knew of Weston Price's research on traditional diets, and his argument that the degenerative "diseases of civilization" were produced by the simplified diets that are characteristic of the highly industrialized societies.

The main bulk of an animal's body consists of water, protein, fat and bones. Fat tissue and bone are metabolically more quiescent than the protein-water systems. During stress or starvation, or even hibernation, animals lose lean mass faster than fat.

The amino acids that constitute protein have many hormone-like functions in their free state. When our glucose (glycogen) stores have been depleted, we convert our own tissue into free amino acids, some of which are used to produce new glucose. The amino acids cysteine and tryptophan, released in large quantities during stress, have antimetabolic (thyroid-suppressing) and, eventually, toxic effects. Hypothyroidism itself increases the catabolic turnover of protein, even though general metabolism is slowed.

Other amino acids act as nerve-modifiers ("transmitters"), causing, for example, excitation or inhibition.

Some of these amino acids, such as glycine, have a very broad range of cell-protective actions.

Their physical properties, rather than their use for production of energy or other metabolic function, are responsible for their important cytoprotective actions.

Gelatin (the cooked form of collagen) makes up about 50 % of the protein in an animal, but a much smaller percentage in the more active tissues, such as brain, muscle, and liver. 35 % of the amino acids in gelatin are glycine, 11 % alanine, and 21 % proline and hydroxyproline.

In the industrialized societies, the consumption of gelatin has decreased, relative to the foods that contain an inappropriately high proportion of the antimetabolic amino acids, especially tryptophan and cysteine.

The degenerative and inflammatory diseases can often be corrected by the use of gelatin-rich foods.

As I began to study endocrinology, I realized that there were some radical misconceptions behind the ideas of "scientific nutrition." I. P. Pavlov, who had studied nutritional physiology because it constituted the animal's closest interactions with its environment, was motivated by a desire to understand life in its totality, including consciousness. But western nutritionists were nearly all committed to an ideology that forced them to think in terms of "essential factors for growth," leading to ideas such as "minimum daily requirement" for each nutrient. Bodily bulk (especially body length) was the criterion, not the experienced quality of life. And there has been no scarcity of evidence showing that rapid bodily growth has its drawbacks ("Big mice die young"[1]).

One of the brightest of the genetically oriented nutritionists, Roger Williams, used the idea of genetic individuality to explain that the popular idea of a species-wide standard diet couldn't be applied to exceptional individuals, and that disease was often the result of the mismatch between special nutritional requirements and a "standard" diet. Linus Pauling's concept of orthomolecular medicine was a restatement of Williams' principle for the general scientific community.

But still, the emphasis was on the match between a specific chemical and the genetic constitution of the organism. Pavlov's idea of the "trophic" actions of nerves was discarded, and the rest of his work was relegated to a crudely caricatured branch of psychology. His therapeutic recommendation of beef broth for many ailments was ignored as having nothing to do with the caricatured "Pavlovism."

If nerves are intimately involved in the processes of nutrition and development, the effects of nutrients on the nerves and their development should have a central place in nutritional research. Our appetites reflect our biochemical needs, and our "unconditional reflexes" are likely to be wiser than the theories that are based simply on the amount of weight a young animal gains on a particular diet.

When I began teaching endocrinology, some of my students didn't want to hear about anything except "lock and key" endocrinology, in which "a hormone" signals certain cells that have a suitable receptor for that hormone. But the studies of Hans Selye and Albert Szent-Györgyi made it clear that Pavlov's global, holistic approach to the organism in its environment was the soundest scientific basis for physiology, including endocrinology. A cell's response to a hormone depended on the state of the cell. Nutrients and metabolites and hormones and neurotransmitters

all modify the cell's sensitivity to its surroundings. The assumptions of "molecular biology," as generally understood, are fundamentally mistaken.

The idea of fixed requirements for specific nutrients, and especially the idea that rapid physical growth was the way to determine the essentiality of a substance, led to a monstrous distortion of the official dietary recommendations. Business, industry, government, and the health professions collaborated in the propagation of an ideology about nutrition that misrepresented the nature of the living organism.

Most studies of the nutritional requirements for protein have been done for the agricultural industries, and so have been designed to find the cheapest way to get the maximum growth in the shortest time. The industry isn't interested in the longevity, intelligence, or happiness of their pigs, chickens, and lambs. The industry has used chemical growth stimulants in combination with the foods that support rapid growth at least expense. Antibiotics and arsenic and polyunsaturated fatty acids have become part of our national food supply because they produce rapid weight gain in young animals.

The amino acids in proteins have been defined as "essential" on the basis of their contribution to growth, ignoring their role in producing long life, good brain development, and good health. The amino acid and protein requirements during aging have hardly been studied, except in rats, whose short life-span makes such studies fairly easy. The few studies that have been done indicate that the requirements for tryptophan and cysteine become very low in adulthood.

Although Clive McKay's studies of life extension through caloric restriction were done in the 1930s, only a few studies have been done to find out which nutrients' restriction contributes most to extending the life span. Restricting toxic heavy metals, without restricting calories, produces about the same life-extending effect as caloric restriction. Restricting only tryptophan, or only cysteine, produces a greater extension of the life span than achieved in most of the studies of caloric restriction. How great would be the life-span extension if both tryptophan and cysteine were restricted at the same time?

Both tryptophan and cysteine inhibit thyroid function and mitochondrial energy production, and have other effects that decrease the ability to withstand stress. Tryptophan is the precursor to serotonin, which causes inflammation, immunodepression, and generally the same

changes seen in aging. Histidine is another amino acid precursor to a mediator of inflammation, histamine; would the restriction of histidine in the diet have a longevity promoting effect, too?

It happens that gelatin is a protein which contains no tryptophan, and only small amounts of cysteine, methionine, and histidine. Using gelatin as a major dietary protein is an easy way to restrict the amino acids that are associated with many of the problems of aging.

The main amino acids in gelatin are glycine and proline; alanine is also present in significant quantity. Glycine and proline are responsible for the unusual fibrous property of collagen.

An animal's body, apart from fat and water, is mostly protein, and about half of the protein in the body is collagen (which is the native, uncooked form of gelatin). Its name is derived from its traditional use as glue. It is responsible for the structural toughness of mature animal bodies.

When cells are stressed, they form extra collagen, but they can also dissolve it, to allow for tissue remodeling and growth. Invasive cancers over-produce this kind of enzyme, destroying the extracellular matrix which is needed for normal cellular differentiation and function. When collagen is broken down, it releases factors that promote wound healing and suppress tumor invasiveness.[2] Glycine itself is one of the factors promoting wound healing and tumor inhibition.

It has a wide range of antitumor actions, including the inhibition of new blood vessel formation (angiogenesis), and it has shown protective activity in liver cancer and melanoma. Since glycine is non-toxic (if the kidneys are working, since any amino acid will contribute to the production of ammonia), this kind of chemotherapy can be pleasant.

When we eat animal proteins in the traditional ways (for example, eating fish head soup, as well as the muscles, or "head-cheese" as well as pork chops, and chicken-foot soup as well as drumsticks), we assimilate a large amount of glycine and gelatin. This whole-animal balance of amino acids supports all sorts of biological process, including a balanced growth of children's tissues and organs.

When only the muscle meats are eaten, the amino acid balance entering our blood stream is the same as that produced by extreme stress, when cortisol excess causes our muscles to be broken down to provide energy and material for repair. The formation of serotonin is increased by the excess tryptophan in muscle, and serotonin stimulates

the formation of more cortisol, while the tryptophan itself, along with the excess muscle-derived cysteine, suppresses the thyroid function.

A generous supply of glycine/gelatin, against a balanced background of amino acids, has a great variety of antistress actions. Glycine is recognized as an "inhibitory" neurotransmitter, and promotes natural sleep. Used as a supplement, it has helped to promote recovery from strokes and seizures, and to improve learning and memory. But in every type of cell, it apparently has the same kind of quieting, protective antistress action. The range of injuries produced by an excess of tryptophan and serotonin seems to be prevented or corrected by a generous supply of glycine. Fibrosis, free radical damage, inflammation, cell death from ATP depletion or calcium overload, mitochondrial damage, diabetes, etc., can be prevented or alleviated by glycine.

Some types of cell damage are prevented almost as well by alanine and proline as by glycine, so the use of gelatin, rather than glycine, is preferable, especially when the gelatin is associated with its normal biochemicals. For example, skin is a rich source of steroid hormones, and cartilage contains "Mead acid," which is itself antiinflammatory.

The other well-studied inhibitory neurotransmitter is GABA, so it's significant that GABA (gamma amino butyric acid) is a close analog of glycine (alpha amino acetic acid). A synthetic molecule structurally similar to those natural inhibitory "transmitters," beta amino propanoic acid, has some of the protective effects of glycine and GABA. The other molecules in the series, at least up to epsilon amino caproic acid, have some of the same antiinvasive, antiinflammatory, anti-angiogenic, properties. Alanine and proline, with cell-protecting actions, have the same basic composition, carbon (CH_2 or CH) atoms separating acid and amino groups. Even the amino acids in which the lipophilic carbon atoms extend out in a branched side-chain, valine, leucine, and isoleucine, have some of the antiseizure (inhibitory) action[3,4] of GABA and glycine. Tests done with one, or a few, of the relatively lipophilic (aliphatic) amino acids prevent seizures, while the "balanced" mixtures of amino acids permit seizures; unfortunately, results of this sort haven't led researchers to question the idea of "balance" that developed within the setting of agricultural research.

The similarity between the structures and actions of glycine and GABA suggest that their "receptors" are similar, if not identical. For years, it has been known that progesterone and pregnenolone act on the

GABA receptor, to reinforce the protective, inhibitory effects of GABA. Estrogen has the opposite effect, inhibiting GABA's action. Since GABA opposes estrogen and inhibits the growth of breast cancer, it wouldn't be surprising if glycine, alanine, etc., did the same.

Recent research shows that progesterone and its metabolites also act on the "glycine receptor," increasing inhibition, and that the "phytoestrogen," genistein, antagonizes the inhibitory effect of glycine.

The inhibitory systems are opposed by excitatory systems, especially by the excitatory amino acid system, activated by glutamic and aspartic acid. Progesterone and estrogen act on that system, too, decreasing and increasing excitation, respectively.

I have previously discussed the arguments for viewing progesterone as a "cardinal adsorbent" (as in Ling and,[5,6] Ling, et al., 1984, a steroid alters glycine's influence on the cell's electrical behavior) which increases the lipophilic, fat-loving property of the cytoplasm, and estrogen as having the opposite action, increasing the water-loving hydrophilic quality of the cytoplasm. If we think of the proteins known as the GABA and glycine receptors as having some regions in which the basic amine of lysine associates with the acidic group of aspartic or glutamic acid, then the action of glycine, or other amino acids would be to introduce additional lipophilic carbon atoms into those regions (with the amino acids' polar ends pairing with their opposites on the protein), where the cardinal adsorbents exert their influence.

Generally, biologists seem puzzled by such facts, because they don't fit into the "lock and key" model of molecular biology. But I think they make the organism easier to understand, since these constellations of facts illustrate simple and general physical principles. They suggest the idea that estrogen and progesterone and glycine, GABA, etc., will be active in any functioning cell, at a suitable concentration. It was this kind of thinking in terms of general physical principles that led Szent-Györgyi to investigate the effects of estrogen and progesterone on heart physiology. The old characterization of estrogen and progesterone as "sex" and "pregnancy" hormones acting on a few tissues through specific receptors never had a good basis in evidence, but the accumulated evidence has now made those ideas impossible for an informed person to accept. (Progesterone increases the heart's pumping efficiency, and estrogen is antagonistic, and can produce cardiac arrhythmia.)

In the context of the excitatory actions of estrogen, and the inhibitory action of glycine, it would be reasonable to think of glycine as one of the antiestrogenic substances. Another type of amino acid, taurine, is structurally similar to glycine (and to beta amino propanoic acid, and to GABA), and it can be thought of as antiestrogenic in this context. The specific kinds of excitation produced by estrogen that relate to reproduction occur against a background of very generalized cellular excitation, that includes increased sensitivity of sensory nerves, increased activity of motor nerves, changes in the EEG, and, if the estrogen effect is very high, epilepsy, tetany, or psychosis.

Glycine's inhibitory effects appear to oppose estrogen's actions generally, in sensory and motor nerves, in regulating angiogenesis, and in modulating the cytokines and "chemokines" that are involved in so many inflammatory and degenerative diseases, especially tumor necrosis factor (TNF), nitric oxide (NO), and prostaglandins. Exposure to estrogen early in life can affect the health in adulthood, and so can an early deficiency of glycine. The degenerative diseases can begin in the earliest years of life, but because aging, like growth, is a developmental process, it's never too late to start the corrective process.

One of estrogen's "excitatory" effects is to cause lipolysis, the release of fatty acids from storage fat; it directs the conversion of glucose into fat in the liver, so that the free fatty acids in the circulation remain chronically high under its influence. The free fatty acids inhibit the oxidation of glucose for energy, creating insulin resistance, the condition that normally increases with aging, and that can lead to hyperglycemia and "diabetes."

Gelatin and glycine have recently been reported to facilitate the action of insulin in lowering blood sugar and alleviating diabetes. Gelatin has been used successfully to treat diabetes for over 100 years (A. Guerard, Ann Hygiene 36, 5, 1871; H. Brat, Deut. Med. Wochenschrift 28 (No. 2), 21, 1902). Glycine inhibits lipolysis (another antiexcitatory, "antiestrogenic" effect), and this in itself will make insulin more effective, and help to prevent hyperglycemia. (A gelatin-rich diet can also lower the serum triglycerides.) Since persistent lipolysis and insulin resistance, along with a generalized inflammatory state, are involved in a great variety of diseases, especially in the degenerative diseases, it's reasonable to consider using glycine/gelatin for almost any chronic problem. (Chicken foot soup has been used in several cultures for a variety of ailments;

chicken foot powder has been advocated as a stimulant for spinal cord regeneration—Harry Robertson's method was stopped by the FDA).

Although Hans Selye observed as early as the 1930s that stress causes internal bleeding (in lungs, adrenals, thymus, intestine, salivary and tear glands, etc.), the medical establishment, which has the opportunity to see it after surgery, burns or other trauma, and following strokes and head injuries, prefers to explain it by "stomach hyperacidity," as if it were limited to the stomach and duodenum. And the spontaneous bruising, and easy bruising, that is experienced by millions of women, especially with the premenstrual syndrome, and nose bleeds, and scleral bleeding, purpura senilis, urinary bleeding, bleeding gums, and many other kinds of "spontaneous" or stress related bleeding, are treated by main-line medicine as if they had no particular physiological significance.

Stress is an energy problem, that leads to the series of hormonal and metabolic reactions that I have often written about—lipolysis, glycolysis, increased serotonin, cortisol, estrogen, prolactin, leaky capillaries, protein catabolism, etc. The capillaries are among the first tissues to be damaged by stress.

Although Selye showed that estrogen treatment mimics shock and stress, and that progesterone prevents the stress reaction, the effects of these hormones on the circulatory system have never been treated systematically. Katherina Dalton observed that progesterone treatment prevented the spontaneous bruising of the premenstrual syndrome; Soderwall observed that estrogen caused enlargement of the adrenals, sometimes with hemorrhage and necrosis; old female animals often have bleeding in the adrenals.[7] Strangely, estrogen's induction of uterine bleeding has been compartmentalized, as if the endometrial blood vessels didn't follow the same rules as vessels elsewhere in the body. Both estrogen and cortisol are known to cause clotting disorders and to increase capillary fragility, but these steroids have been elevated to the realm of billion dollar drug products, beyond the reach of ordinary physiological thinking. Other stress-released substances that are entangled in the drug market (tryptophan, serotonin, nitric oxide, and unsaturated fats, for example) are similarly exempt from consideration as factors in circulatory, neoplastic, and degenerative diseases.

At the time Selye was observing stress-induced bleeding, standard medicine was putting gelatin to use—orally, subcutaneously, and intravenously—to control bleeding. Since ancient times, it had been

used to stop bleeding by applying it to wounds, and this had finally been incorporated into medical practice.

The 1936 Cyclopedia of Medicine (G.M. Piersol, editor, volume 6) mentions the use of gelatin solution to quickly control nosebleeds, excessive menstrual bleeding, bleeding ulcers (using three doses of 18 grams as a 10 % solution during one day), and bleeding from hemorrhoids and the lower bowel, and hemorrhage from the bladder. But since Selye's work relating the thrombohemorrhagic syndromes to stress wasn't known at that time, gelatin was thought of as a useful drug, rather than as having potentially far-reaching physiological effects, antagonizing some of the agents of stress-induced tissue damage.

Skin cells and nerve cells and many other cells are "electrically" stabilized by glycine, and this effect is currently being described in terms of a "chloride current." A variety of mechanisms have been proposed for the protective effects of some of the amino acids, based on their use as energy or for other metabolic purpose, but there is evidence that glycine and alanine act protectively without being metabolized, simply by their physical properties.

A small dose of glycine taken shortly after suffering a stroke was found to accelerate recovery, preventing the spreading of injury through its inhibitory and antiinflammatory actions. Its nerve-stabilizing action, increasing the amount of stimulation required to activate nerves, is protective in epilepsy, too. This effect is important in the regulation of sleep, breathing, and heart rhythm.

Glycine's antispastic activity has been used to alleviate the muscle spasms of multiple sclerosis. It is thought to moderate some of the symptoms of schizophrenia.

A recent publication shows that glycine alleviates colitis; but the use of gelatin, especially in the form of a concentrated gelatinous beef broth, for colitis, dysentery, ulcers, celiac disease, and other diseases of the digestive system, goes far back in medical history. Pavlov's observation of its effectiveness in stimulating the secretion of digestive juices occurred because the stimulating value of broth was already recognized.

Although I pointed out a long time ago the antithyroid effects of excessive cysteine and tryptophan from eating only the muscle meats, and have been recommending gelatinous broth at bedtime to stop nocturnal stress, it took me many years to begin to experiment with large amounts of gelatin in my diet. Focusing on the various toxic effects of tryptophan

and cysteine, I decided that using commercial gelatin, instead of broth, would be helpful for the experiment. For years I hadn't slept through a whole night without waking, and I was in the habit of having some juice or a little thyroid to help me go back to sleep. The first time I had several grams of gelatin just before bedtime, I slept without interruption for about 9 h. I mentioned this effect to some friends, and later they told me that friends and relatives of theirs had recovered from long-standing pain problems (arthritic and rheumatic and possibly neurological) in just a few days after taking 10 or 15 g of gelatin each day.

For a long time, gelatin's therapeutic effect in arthritis was assumed to result from its use in repairing the cartilage or other connective tissues around joints, simply because those tissues contain so much collagen. (Marketers suggest that eating cartilage or gelatin will build cartilage or other collagenous tissue.) Some of the consumed gelatin does get incorporated into the joint cartilage, but that is a slow process, and the relief of pain and inflammation is likely to be almost immediate, resembling the antiinflammatory effect of cortisol or aspirin.

Inflammation produces fibrosis, because stress, hypoxia, and inadequate supply of glucose stimulate the fibroblasts to produce increased amounts of collagen. In lungs, kidneys, liver, and other tissues, glycine protects against fibrosis, the opposite of what the traditional view would suggest.

Since excess tryptophan is known to produce muscle pain, myositis, even muscular dystrophy, gelatin is an appropriate food for helping to correct those problems, simply because of its lack of tryptophan. (Again, the popular nutritional idea of amino acids as simply building blocks for tissues is exactly wrong—muscle protein can exacerbate muscle disease.) All of the conditions involving excess prolactin, serotonin, and cortisol (autism, postpartum and premenstrual problems, Cushing's disease, "diabetes," impotence, etc.) should benefit from reduced consumption of tryptophan. But the specifically antiinflammatory amino acids in gelatin also antagonize the excitatory effects of the tryptophan-serotonin-estrogen- prolactin system.

In some of the older studies, therapeutic results improved when the daily gelatin was increased. Since 30 g of glycine was commonly used for treating muscular dystrophy and myasthenia gravis, a daily intake of 100 g of gelatin wouldn't seem unreasonable, and some people find that quantities in that range help to decrease fatigue. For a growing child,

though, such a large amount of refined gelatin would tend to displace other important foods. The National Academy of Sciences recently reviewed the requirements for working adults (male and female soldiers, in particular), and suggested that 100 g of balanced protein was needed for efficient work. For adults, a large part of that could be in the form of gelatin.

If a person eats a large serving of meat, it's probably helpful to have 5 or 10 g of gelatin at approximately the same time, so that the amino acids enter the blood stream in balance.

Asian grocery stores are likely to sell some of the traditional gelatin-rich foods, such as prepared pig skin and ears and tails, and chicken feet.

Although the prepared powdered gelatin doesn't require any cooking, dissolving it in hot water makes it digest a little more quickly. It can be incorporated into custards, mousses, ice cream, soups, sauces, cheese cake, pies, etc., or mixed with fruit juices to make desserts or (with juice concentrate) candies.

Although pure glycine has its place as a useful and remarkably safe drug, it shouldn't be thought of as a food, because manufactured products are always likely to contain peculiar contaminants.

Genes, Carbon Dioxide, and Adaptation

Ray Peat's Newsletter, 2012

> "Over the oxygen supply of the body carbon dioxide spreads its protecting wings."
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> — Friedrich Miescher, Swiss physiologist, 1885

To reach useful simplicities, we usually have to sift through the accumulated rationalizations previous generations have produced to justify doing things their way. If we could start with an accurate understanding of what life is, and what we are doing here, science could be built up deductively as well as by the accumulation of evidence. But the fact that we have grown up amid false and unworkable models of what life is, means that we have to lean heavily on evidence, building up new models inductively, imaginatively, and scientifically. Textbooks and professional journals can be useful if they are seen as monuments to past beliefs, and not as authorities to be accepted. Examining the dogmatic models of life and the world in which life exists, we can better understand the nature of the existing barriers to constructive work.

The Central Dogma of the molecular geneticists, in their own words, was that information flows only from DNA to RNA, and from RNA to protein, never in the other direction. The Central Dogma was formulated to suppress forever the Lamarckian idea of the inheritance of acquired characters, that Weismann's amputation of the tails of a multitude of mice had attempted to deal with earlier in the history of genetics.

The Central Dogma continues to be influential, even after a series of revisions. Until the 1990s, the only "practical" fruit of genetics had been genocide, but now it has become possible to insert genes into bacteria, and to use the bacteria to produce industrial quantities of specific proteins. In principle, that could be useful, although bovine growth hormone poses a threat to the health of both people and cows, human growth hormone poses a threat to athletes and old people, and human insulin could increase the number of treated diabetics. A deranged culture will put anything cheap to bad use. The ability to make organisms

produce foreign proteins confirms that information can flow from DNA to protein, but as that technology was being developed, the discovery of retroviruses showed that the Central Dogma of molecular genetics was wrong, RNA is a very significant template for the production of DNA. And the scrapie prion shows that proteins can be infectious, passing along information without nucleic acids as the agent of transmission. The directed mutations demonstrated by John Cairns and others have thoroughly destroyed the Central Dogma of molecular genetics, even as it applied to the simplest organisms, but molecular genetics survives as an industrial and forensic technology.

Although evidence suggests that about 2% of human diseases involve the inheritance of an abnormal protein, the exact way the disease develops is never as clear as the geneticists would imply. And the major diseases, cancer, diabetes, heart disease, Alzheimer's, epilepsy, depression, etc., that are so often blamed on "genes," are so poorly understood that it is arbitrary and crazy to talk about the way genes "cause" them. People who had never had a problem with diabetes in their culture, very soon suffered from the same rate of diabetes as their neighbors when they immigrated into Israel and began eating the European style diet. The interesting thing about the genetic explanation for disease is how its proponents can believe what they are saying. If you read Konrad Lorenz's writings on racial hygiene, you can imagine that he might have really come to believe what he was saying, even if it was an invention that earned him personal prestige and revenge against people who were reluctant to accept his ideas of cultural excellence and inferiority. When I listened to Gunther Stent praising the doctrine he had taken straight from Konrad Lorenz's original genocide papers, I wondered how a German who had escaped the holocaust with his Jewish family when he was nine years old could talk about those doctrines without anger, and without pointing out the purpose for which they had been created. In the audience, a professor who had been a refugee from Hungary defended the doctrine, saying that a man and his work have nothing to do with each other, though the whole content of the doctrine was that a man and his work are identical, because his behavior is determined by his genes. These were mature, internationally known intellectuals, who made the most amazingly self-contradictory statements without embarrassment, because they were committed, for some deep, mysterious reason, to the doctrine of genetic determinism. If these refugees could espouse the

rationale for "racial hygiene" as their own, I suppose it isn't so hard to understand that people can devote their life to studying the genetics of diabetes, even though diabetes has appeared suddenly in one generation of immigrants when their diet was suddenly changed, a massive fact that bluntly contradicts the genetic doctrine. There is something very deep in our culture that loves genetics.

One of the cultural trends that makes genetic determinism attractive is the theory of radical individualism, something that has grown up with protestant Christianity, according to some historians. Roger Williams' work in nutrition seemed to be powered by this idea of individual genetic uniqueness, and in his case, the idea led him to some useful insights—he suggested that the environment could be adjusted to suit the highly specific needs of the individual. This idea led to the widespread belief that nutritional supplements might be needed by a large part of the population. Extreme nurturing of the deviant individual is the opposite extreme from the Lorenzian-Hitlerian solution, of eliminating everyone who wasn't a perfect Aryan specimen.

But Williams' genetic doctrine assumed that our nutritional needs were primarily inborn, determined by our unique genes. However, there is a famous experiment in which rats were made deficient in riboflavin, and when their corneal tissue showed evidence of the vitamin deficiency, they were given a standard diet. However, the standard diet no longer met the needs of their eye tissue, and during the remainder of the observation period, only a dose of riboflavin several times higher than normal would prevent the signs of deficiency. A developmental change had taken place in the cornea, making its vitamin B_2 requirement abnormally high. If we accept the epigenetic, developmental idea of metabolic requirements, our idea of nurturing environmental support would consider the long-range effects of environmental adequacy, and would consider that much disease could be prevented by prenatal support, and by avoiding extreme deficiencies at any time. Williams himself emphasized the importance of prenatal nutrition in disease prevention, so he wasn't a genetic totalitarian; combining the idea of unique genetic individuality with the recognition that malnutrition causes disease, led him to believe in the necessity for nutritional adequacy, rather than to the extermination of the sick, weak, or different individuals.

The idea of "genetic determinism" says that our traits are the result of the specific proteins that are produced by our specific genes. The

doctrine allows for some gradations, such as "half a dose" of a trait, but in practice it becomes a purely subjective accounting for everything in terms of mysterious degrees of "penetrance" of genes, and interactions with unknown factors. Proteins, that supposedly express our genetic constitution, include enzymes, structural proteins, antibodies, and a variety of protein hormones and peptide regulatory molecules. Every protein, including the smallest peptide (except certain cyclic peptides), contains at least one amine group, and usually several. Amine groups react spontaneously with carbon dioxide, to form carbamino groups, and they can also react, nonenzymically, with sugars, in the reaction called glycation or glycosylation. These chemical changes alter the functions of the proteins, so that hormones and their "receptors," tubules and filaments, enzymes and synthetic systems, all behave differently under their influences. (The proteins' electrical charge, relationship to water and fats, and shape, change quickly and reversibly as the concentration of carbon dioxide changes; in the absence of carbon dioxide, these properties tend to change irreversibly under the influence of metabolic stress.)

This is the clearest, and the most powerful, instance of metabolic influence on biological structure. That makes it very remarkable that it has been the subject of so few publications. I think the absence of discussion of this fundamental biological principle can be understood only in relation to the great importance it has for a new understanding of development and inheritance—it is an easily documented process that will invalidate some of the most deeply held beliefs of most of the people who are influential in science and politics.

I will continue discussing some of these implications in newsletters on imprinting, degenerative diseases, heart attacks, high blood pressure, and other special biological questions, but I think the most important work that remains to be done is to work out the exact mechanisms by which metabolic energy, expressed largely by factors such as the ratio of carbon dioxide to lactic acid, guides both development and evolution. These ideas will have to take into account the actual resources of the world, as well as the internal processes and resources of the organism. Each development in the organism, whether it leads to maturation or to degeneration, consists of responses to and interactions with specific environments.

Curiosity, esthetics, creativity, and stimulation are necessarily and deeply linked to metabolic efficiency and structural-anatomical development. For example, the known effects of stimulation and success (or isolation and depression) on brain anatomy and function should be linked meaningfully with metabolic, hormonal and dietary processes. There is a large amount of information available that could be put to practical use, but there are still important ideological barriers to be overcome. Marshalling the information needed to optimize our own development runs counter to the program of our technical-scientific culture, which prefers to believe that degeneration is programmed, while emergent evolution is unforeseeable. But, if an optimization project is presented as a way to forestall the "programmed degeneration," it might succeed in becoming part of the culture.

Vernadsky's idea of the Noosphere differs from the Gaia hypothesis (that the world is a self-regulating organism-like system) in the intrinsic directionality of Vernadsky's Noosphere, which makes the course of human society crucial for the fate of the planet. It proposes that planets, like organisms, are going somewhere. The Gaia hypothesis is increasingly being interpreted as a justification for feeling no responsibility for the effects of technology on the environment, and some people are expressing that view of the world as essentially a justification for any vandalism that may come along. Kary Mullis, for example, says that mass extinctions of organisms have occurred in the past, and so it's just natural for species to become extinct, and it isn't appropriate to be concerned about the extinctions that are being caused by civilization's technological depredations.

In the Noosphere, global warming and increased carbon dioxide would represent an advance toward a higher state of "metabolism" of the world, and this would support the emergence of new biological forms from those existing. But if whole systems of life are destroyed before that happens, the biological achievements of the past could be lost irretrievably; there is no guarantee that the system will continue to work, if major sectors are deleted from the interacting systems. Even in terms of the Gaia conception, that the earth is like an organism, consider what the loss of genetic complexity means for an organism. Sometimes, for example, things that happen to an individual lead to sterility several generations later, although the procedure didn't seem lethal for the individual or its immediate descendants.

The whole idea of "evolution" is that the past is preserved within the present, or that the present is built upon the accomplishments of the past. The idea that evolution has been "random," and that the world is simply self-regulating, might seem liberating to those who hate the idea that they might be intrinsically responsible for anything outside of themselves, but it is liberating only in the way that a vandal's manifesto might be, declaring the world to be their playground.

The problem with such a manifesto of irresponsibility is simply that it is built upon the same system of cultural assumptions that produced Nazi eugenics, and that those assumptions are false. The political assumptions of the people who controlled scientific institutions were built into a set of pseudo-scientific doctrines, which continue to be valued for their political and philosophical implications.

For hundreds or thousands of years, the therapeutic value of carbonated mineral springs has been known. The belief that it was the water's lively gas content that made it therapeutic led Joseph Priestley to investigate ways to make artificially carbonated water, and in the process he discovered oxygen. Carbonated water had its medical vogue in the 19th century, but the modern medical establishment has chosen to define itself in a way that glorifies "dangerous," "powerful" treatments, and ridicules "natural" and mild approaches. The motivation is obvious—to maintain a monopoly, there must be some reason to exclude the general public from "the practice of medicine." Witch doctors maintained their monopoly by working with frightening ghost-powers, and modern medicine uses its technical mystifications to the same purpose. Although the medical profession hasn't lost its legal monopoly on health care, corporate interests have come to control the way medicine is practiced, and the way research is done in all the fields related to medicine.

The fact that carbon dioxide therapy is extremely safe has led to the official doctrine that it can't be effective. The results reviewed by Yandell Henderson in the Cyclopedia of Medicine in 1940 were so impressive that carbon dioxide therapy would have been as commonly used and as well known as oxygen therapy, radiation treatments, sulfa drugs, barbiturates, and digitalis, but it was completely lacking in the thrilling mystique of those dangerous treatments.

Henderson assumed that carbon dioxide use was becoming a permanent part of medicine, to be used with anesthesia to prevent cessation of spontaneous breathing, during recovery from surgery to prevent shock

and pneumonia, for stimulating respiration in newborns, and for resuscitating drowning or suffocation victims, as well as for treatment of heart disease and some neurological conditions (see below). However, its use in surgery and resuscitation has probably decreased since he wrote, despite occasional publications pointing out the dangers involved in the use of oxygen without carbon dioxide.

Glucose and Sucrose for Diabetes

Ray Peat's Newsletter, 2012

DIABETES has been known since ancient times as a wasting disease in which sugar was lost in the urine, but more recently the name has been used to describe the presence of more than the normal amount of glucose in the blood, even in the absence of glucose in the urine. Some of the medical ideas regarding the original form of the condition have been applied to the newer form.

Cultural "paradigms" or ideologies are so convenient that people often don't bother to doubt them, and they are sometimes so rigorously enforced that people learn to keep their doubts to themselves. Public concern about diabetes has been growing for decades, but despite the introduction of insulin and other drugs to treat it, and massive campaigns to "improve" eating habits, mortality from diabetes has been increasing during the last 100 years. Diabetes ("type 1") has been increasing even among children.[1]

A basic meaning of homeopathic medicine is the support of the organism's ability to heal itself; the essence of allopathy is that the physician fights "a disease" to cure the patient, e.g., by cutting out tumors or killing germs.

Confidence in the organism's essential rationality led the doctors with a homeopathic orientation to see a fever as part of a recuperative process, while their allopathic opponents sometimes saw fever as the essence of the sickness to be cured. Homeopaths concentrated on the nature of the patient; allopaths concentrated on a disease entity in itself, and were likely to ignore the patient's idiosyncrasies and preferences.

Diabetes was named for the excessive urination it causes, and for the sugar in the urine. It was called the sugar disease, and physicians were taught that sugar was the problem. Patients were ordered to avoid sweet foods, and in hospitals they were sometimes locked up to keep them from finding sweets. The practice was derived from ideology, not from any evidence that the treatment helped.

In 1857, M. Piorry in Paris and William Budd in Bristol, England, reasoned that if a patient was losing a pound of sugar every day in 10 liters of urine, and was losing weight very rapidly, and had an intense craving for sugar, it would be reasonable to replace some of the lost sugar,

simply because the quick weight loss of diabetes invariably led to death. Keeping patients from eating what they craved seemed both cruel and futile.

After Budd's detailed reports of a woman's progressive recovery over a period of several weeks when he prescribed 8 ounces of sugar every day, along with a normal diet including beef and beef broth, a London physician, Thomas Williams, wrote sarcastically about Budd's metaphysical ideas, and reported his own trial of a diet that he described as similar to Budd's. But after two or three days he decided his patients were getting worse, and stopped the experiment.

Williams' publication was presented as a scientific refutation of Budd's deluded homeopathic ideas, but Budd hadn't explained his experiment as anything more than an attempt to slow the patient's death from wasting which was sure to be the result of losing so much sugar in the urine. The following year Budd described another patient, a young man who had become too weak to work and who was losing weight at an extreme rate. Budd's prescription included 8 ounces of white sugar and 4 ounces of honey every day, and again, instead of increasing the amount of glucose in the urine, the amount decreased quickly as the patient began eating almost as much sugar as was being lost initially, and then as the loss of sugar in the urine decreased, the patient gained weight and recovered his strength.

Drs. Budd and Piorry described patients recovering from an incurable disease, and that has usually been enough to make the medical profession antagonistic. Even when a physician has himself diagnosed diabetes and told a patient that it would be necessary to inject insulin for the rest of his life, if that patient recovers by changing his diet, the physician will typically say that the diagnosis was wrong, because diabetes is incurable.

Twenty-five years ago, some rabbits were made diabetic with a poison that killed their insulin-secreting pancreatic beta-cells, and when some of them recovered from the diabetes after being given supplemental DHEA, it was found that their beta-cells had regenerated. The more recent interest in stem cells has led several research groups to acknowledge that in animals the insulin-producing cells are able to regenerate.

It is now conceivable that there will be an effort to understand the factors that damage the beta-cells, and the factors that allow them to

regenerate. The observations of Budd and Piorry would be a good place to start such a reconsideration.

For many years, physicians have been taught that diabetes is either "genetic" or possibly caused by a viral infection, that might trigger an "autoimmune reaction," but the study of cellular respiration and energy metabolism and endocrinology has provided more convincing explanations. The antibodies that are found in the "autoimmune" conditions are evidence of tissue damage, but the damage may have been done by metabolic toxins, with the immune system's involvement being primarily the removal of defective cells.

In the 1940s, Bernardo Houssay found that coconut oil protected animals from poison-induced diabetes, while a lard-based diet failed to protect them. Later, glucose itself was found to protect the pancreatic beta-cells from poisons.

In 1963, P.J. Randle clearly described the inhibition of glucose oxidation by free fatty acids. Later, when lipid emulsions came into use for intravenous feeding in hospitals, it was found that they blocked glucose oxidation, lowered the metabolic rate, suppressed immunity, and increased lipid peroxidation and oxidative stress.

Estrogen and stress are both known to create some of the conditions of diabetes, while increasing fat oxidation and inhibiting glucose oxidation. Emotional stress, overwork, trauma, and infections have been known to initiate diabetes. Estrogen increases free fatty acids and decreases glycogen storage, and when birth control pills were becoming popular, some researchers warned that they might cause diabetes. But the food oil industry and the estrogen industry were satisfied with the medical doctrine that diabetes was caused by eating too much sugar.

If the essence of diabetes is the presence of too much sugar, then it seems reasonable to argue that it is the excess sugar that's responsible for the suffering and death associated with the disease, otherwise, how would the prohibition of sugar in the diet be justified? In fact, the argument is made[2] that it is the hyperglycemia that causes problems such as hypertension, kidney failure, heart failure, neuropathy, blindness, dementia, and gangrene.

As information about the many physiological and biochemical events associated with diabetes has accumulated, the basic doctrine that "sugar causes diabetes" has extended itself to whatever the topic of discussion is: "Glucose causes" the death of beta-cells, glucose causes blood vessels

to become leaky, glucose causes cells to be unable to absorb glucose, glucose causes the formation of free radicals, glucose impairs immunity and wound healing, but causes inflammation while preventing the "respiratory burst" in which free radicals are produced by cells that cause inflammation, it disturbs enzyme functions, impairs nerve conduction and muscle strength, etc., and it is also addictive, causing people to irrationally seek the very material that is poisoning them.

Tens of thousands of publications describe the pathogenic effects of sugar. To prove their point, they grow cells in a culture dish, and find that when they are exposed to excess glucose, often 5 times the normal amount, they deteriorate. In the artificial conditions of cell culture, the oversupply of glucose causes lactic acid to accumulate, leading to toxic effects. But in the organism, the hyperglycemia is compensating for a sensed deficiency of glucose, a need for more energy.

If diabetes means that cells can't absorb or metabolize glucose, then any cellular function that requires glucose will be impaired, despite the presence of glucose in the blood. It is the intracellular absence of glucose which is problematic, rather than its extracellular excess.

Neuroglycopenia (or neuroglucopenia) or intracellular glycopenia refers to the deficit of glucose in cells. When the brain senses a lack of glucose, nerves are activated to increase the amount of glucose in the blood, to correct the problem. As long as the brain senses the need for more glucose, the regulatory systems will make the adjustments to the blood glucose level.

The antagonism between fat and sugar that Randle described can involve the suppression of sugar oxidation when the concentration of fats in the bloodstream is increased by eating fatty food, or by releasing fats from the tissues by lipolysis, but it can also involve the suppression of fat oxidation by inhibiting the release of fatty acids from the tissues, when a sufficient amount of sugar is eaten.

When a normal person, or even a "type 2 diabetic," is given a large dose of sugar, there is a suppression of lipolysis, and the concentration of free fatty acids in the bloodstream decreases, though the suppression is weaker in the diabetic.[3] Insulin, released by the sugar, inhibits lipolysis, reducing the supply of fats to the respiring cells.

Free fatty acids suppress mitochondrial respiration,[4] leading to increased glycolysis (producing lactic acid) to maintain cellular energy. The suppression of mitochondrial respiration increases the production

of toxic free radicals, and the decreased carbon dioxide makes the proteins more susceptible to attack by free radicals. The lactate produced under the influence of excessive fat metabolism stimulates the release of endorphins, which are lipolytic, releasing more free fatty acids from the tissues. Acting through cytokines such as interleukin-6, lactate shifts the balance toward the catabolic hormones, leading to tissue wasting.

Lactic acid itself, and the longer chain fatty acids, inhibit the regulatory enzyme pyruvate dehydrogenase (which is activated by insulin), reducing the oxidative production of energy. Drugs to activate this enzyme are being studied by the pharmaceutical industry as treatments for diabetes and cancer (for example, DCA, dichloroacetate).

Oxidative damage of proteins is often described as glycation or glycosylation, but it really consists of many addition and crosslinking reactions, most often onto, or between, lysine groups. Carbon dioxide normally associates with lysine groups, so the destructive reactions are favored when carbon dioxide is displaced by lactic acid. The reactive fragments of polyunsaturated fatty acids are much more often the source of the protein-damaging radicals than the carbohydrates are.

The importance of the fats in causing type-2 diabetes is coming to be accepted, for example Li, et al., recently (2008) said "The cellular link between fatty acids and ROS (reactive oxygen species) is essentially the mitochondrion, a key organelle for the control of insulin secretion. Mitochondria are the main source of ROS and are also the primary target of oxidative attacks."

But much earlier[5] it had been demonstrated that a deficiency of the "essential fatty acids" prevents toxin-induced diabetes and greatly increases resistance to inflammation.[6] The lack of those so-called "essential fatty acids" also prevents autoimmune diabetes in a strain of diabetic mice.[7]

Suppressing fatty acid oxidation improves the contraction of the heart muscle and increases the efficiency of oxygen use.[8] Various drugs are being considered for that purpose, but niacinamide is already being used to improve heart function, since it lowers the concentration of free fatty acids.

The antimetabolic and toxic effects of the polyunsaturated fatty acids can account for the "insulin resistance" that characterizes type-2 diabetes, but similar actions in the pancreatic beta-cells can impair or kill those cells, creating a deficiency of insulin, resembling type-1 diabetes.

The suppression of mitochondrial respiration causes increased free radical damage, and the presence of polyunsaturated fatty acids in the suppressed cell increases the rate of fat decomposition and production of toxins.

Increasing the rate of respiration by replacing the fats with glucose reduces the availability of electrons that can trigger lipid peroxidation and produce toxic free radicals, and the shift of fuel also increases the amount of carbon dioxide produced, which can protect the protein amino groups such as lysine from glycation and lipoxidation.

While it's clear that it is the excessive oxidation of fat that damages cells in the "diabetic" state in which cells aren't able to use glucose, it's important to look at some of the situations in which so many researchers are blaming problems on hyperglycemia.

Important problems in diabetes are slow wound healing, excessive permeability or leakiness of blood vessels which allows molecules such as albumin to be extravasated, and the impaired function and survival of pancreatic beta-cells.

During the healing of a wound in a diabetic individual, the local concentration of glucose decreases and then entirely disappears, as healing stops. Applying glucose and insulin topically to the wound, it heals quickly. The very old practice of treating deep wounds with honey or granulated sugar has been studied in controlled situations, including the treatment of diabetic ulcers, infected deep wounds following heart surgery, and wounds of lepers. The treatment eradicates bacterial infections better than some antiseptics, and accelerates healing without scarring, or with minimal scarring. The sugar regulates the communication between cells, and optimizes the synthesis of collagen and extracellular matrix.

An excess of insulin, causing hypoglycemia, can cause blood vessels, for example in the brain and kidneys, to become leaky, and this has been claimed to be an effect of insulin itself. However, the same leakiness can be produced by an analog of glucose that can't be metabolized, so that intracellular glycopenia is produced. The harmful effect that has been ascribed to excessive insulin can be prevented by maintaining an adequate supply of glucose,[9] showing that it is the lack of glucose, rather than the excess insulin, that causes the vascular malfunction. Fructose also reduces the leakiness of blood vessels.[10] Many of the complications of diabetes are caused by increased vascular leakiness.[11]

Sugar can protect the beta-cells from the free fatty acids, apparently in the same ways that it protects the cells of blood vessels, restoring metabolic energy and preventing damage to the mitochondria. Glucose suppresses superoxide formation in beta-cells[12] and apparently in other cells including brain cells.[13]

The beta-cell protecting effect of glucose is supported by bicarbonate and sodium. Sodium activates cells to produce carbon dioxide, allowing them to regulate calcium, preventing overstimulation and death. For a given amount of energy released, the oxidation of glucose produces more carbon dioxide and uses less oxygen than the oxidation of fatty acids.

The toxic excess of intracellular calcium that damages the insulin-secreting cells in the relative absence of carbon dioxide is analogous to the increased excitation of nerves and muscles that can be produced by hyperventilation.

In every type of tissue, it is the failure to oxidize glucose that produces oxidative stress and cellular damage. Even feeding enough sucrose to cause fat deposition in the liver can protect the liver from oxidative stress,[14] possibly by mechanisms such as those involved in the treatment of alcoholic liver disease with saturated fats.

The active thyroid hormone, T_3, protects the heart by supporting the oxidation of glucose.[15] The amount of T_3 produced by the liver depends mainly on the amount of glucose available.

Animals that have been made diabetic with relatively low doses of the poison streptozotocin can recover functional beta-cells spontaneously, and the rate of recovery is higher in pregnant animals.[16] Pregnancy stabilizes blood sugar at a higher level, and progesterone favors the oxidation of glucose rather than fats.

A recent study suggests that recovery of the pancreas can be very fast. A little glucose was infused for 4 days into rats, keeping the blood glucose level normal, and the mass of beta-cells was found to have increased 2.5 times. Cell division wasn't increased, so apparently the additional glucose was preventing the death of beta-cells, or stimulating the conversion of another type of cell to become insulin-secreting beta-cells.[17]

That study is very important in relation to stem cells in general, because it either means that glandular cells are turning over ("streaming") at a much higher rate than currently recognized in biology and medicine,

or it means that (when blood sugar is adequate) stimulated cells are able to recruit neighboring cells to participate in their specialized function. Either way, it shows the great importance of environmental factors in regulating our anatomy and physiology.

"Diabetologists" don't regularly measure their patients' insulin, but they usually make the assumption that insulin is the main factor regulating blood sugar. In one study, it was found that the insulin molecule itself, immunoreactive insulin, accounted for only about 8 % of the serum's insulin-like action. The authors of that study believed that potassium was the main other factor in the serum that promoted the disposition of glucose. Since potassium and glucose are both always present in the blood, their effects on each other have usually been ignored.

Cellular activation (by electrical, nervous, chemical, or mechanical stimulation) causes glucose to be absorbed and oxidized, even in the absence of insulin and in otherwise insulin-resistant individuals. I think this local interaction between the need for energy and the production of energy predominates in good health, with insulin and other hormones facilitating the process in times of stress. A variety of local tissue regulators, including GABA and glutamate, probably participate in these interactions, in the brain, endocrine glands, muscles, and other tissues, and are probably involved in the relaxing and analgesic actions of the sugars.

The GABA system (GABA is highly concentrated in the beta-cells) is involved in regulating blood sugar, inhibiting the release of glucagon when glucose isn't needed, and apparently allowing the beta cells to discriminate between amino acids and glucose[18] and acting as a survival and growth factor for neighboring cells.[19]

The damaged beta-cells lose the enzyme (glutamate dehydrogenase) that makes GABA, and their ratio of linoleic acid to saturated and monounsaturated fat increases, a change that corresponds to a decreased metabolism of glucose.

The free intracellular calcium that can become toxic is normally bound safely by well-energized mitochondria, and in the bloodstream it is kept safely complexed with carbon dioxide. The thyroid hormone, producing carbon dioxide, helps to sustain the level of ionized calcium.[20] In a vitamin D deficiency, or a calcium deficiency, the parathyroid hormone increases, and this hormone can contribute to many inflammatory and degenerative processes, including diabetes. Consuming enough calcium

and vitamin D to keep the parathyroid hormone suppressed is important to protect against the degenerative conditions.

When animals were fed an otherwise balanced diet lacking vitamin D, with the addition of either 68 % sucrose or 68 % starch, the bones of those on the starch diet failed to develop normally, as would be expected with a vitamin D deficiency, and their serum calcium was low. However, the bones of those on the diet with sucrose developed properly, and didn't show evidence of being calcium deficient, though they weren't quite as heavy as those that also received an adequate amount of vitamin D.[21] This study suggests that the famous dietetic emphasis on the "complex carbohydrates," i.e., starches, has made an important contribution to the prevalence of osteoporosis, as well as obesity and other degeneration conditions.

Both vitamin D and vitamin K, another important calcium-regulating nutrient, are now known to prevent diabetes. Both of these vitamins require carbon dioxide for disposing of calcium properly, preventing its toxicity. When carbon dioxide is inadequate, for example from simple hyperventilation or from hypothyroidism, calcium is allowed to enter cells, causing inappropriate excitation, sometimes followed by calcification.

Keeping an optimal level of carbon dioxide (for example, when adapted to high altitude) causes calcium to be controlled, resulting in lowered parathyroid hormone, an effect similar to supplementing with calcium, vitamin D, and vitamin K.[22] Glycine, like carbon dioxide, protects proteins against oxidative damage,[23] so including gelatin (very rich in glycine) in the diet is probably protective.

The contribution of PTH to inflammation and degeneration is just being acknowledged,[24] but the mechanism undoubtedly involves the fact that it is lipolytic, increasing the concentration of free fatty acids that suppress metabolism and interfere with the use of glucose.

When we talk about increasing the metabolic rate, and the benefits it produces, we are comparing the rate of metabolism in the presence of thyroid, sugar, salt, and adequate protein to the "normal" diet, containing smaller amounts of those "stimulating" substances. It would be more accurate if we would speak of the suppressive nature of the habitual diet, in relation to the more optimal diet, which provides more energy for work and adaptation, while minimizing the toxic effects of free radicals.

Feeding animals a normal diet with the addition of Coca-Cola, or with a similar amount of sucrose, has been found to let them increase

their calorie intake by 50% without increasing their weight gain.[25] Although plain sucrose can alleviate the metabolic suppression of an average diet, the effect of sugars in the diet is much more likely to be healthful in the long run when they are associated with an abundance of minerals, as in milk and fruit, which provide potassium and calcium and other protective nutrients.

Avoiding the starches such as cereals and beans, and using fruits as a major part of the diet helps to minimize the effects of the polyunsaturated fats.

Celiac disease or gluten sensitivity is associated with diabetes and hypothyroidism. There is a cross reaction between the gluten protein molecule and an enzyme which is expressed under the influence of estrogen. This is another reason for simply avoiding cereal products.

Brewers' yeast has been used traditionally to correct diabetes, and its high content of niacin and other B vitamins and potassium might account for its beneficial effects. However, eating a large quantity of it is likely to cause gas, so some people prefer to extract the soluble nutrients with hot water. Yeast contains a considerable amount of estrogen, and the water extract probably leaves much of that in the insoluble starchy residue. Liver is another rich source of the B vitamins as well as the oily vitamins, but it can suppress thyroid function, so usually one meal a week is enough.

The supplements that most often help to correct diabetes-like conditions are niacinamide, thiamine, thyroid, and progesterone or pregnenolone. Vitamins D and K are clearly protective against developing diabetes, and their effects on many regulatory processes suggest that they would also help to correct existing hyperglycemia.

Drinking coffee seems to be very protective against developing diabetes. Its niacin and magnesium are clearly important, but it is also a rich source of antioxidants, and it helps to maintain normal thyroid and progesterone production. Chocolate is probably protective too, and it is a good source of magnesium and antioxidants.

A recent study[26] showed that inhibition of cholesterol synthesis by beta-cells impairs insulin synthesis, and that replenishing cholesterol restores the insulin secretion. Green tea contains this type of inhibitor, but its use has nevertheless been associated with a reduced risk of diabetes. Caffeine is likely to be the main protective substance in these foods.

Although antioxidants can be protective against diabetes, not all things sold as "antioxidants" are safe; many botannical "antioxidants" are estrogenic. Hundreds of herbal products can lower blood sugar, but many of them are simply toxic, and the reduction of blood glucose can make some problems worse.

The supplements I mention above—including caffeine—have antiinflammatory, antioxidative and energy-promoting effects. Inflammation, interfering with cellular energy production, is probably the essential feature of the things called diabetes.

Aspirin has a very broad spectrum of antiinflammatory actions, and is increasingly being recommended for preventing complications of diabetes. One of the consequences of inflammation is hyperglycemia, and aspirin helps to correct that,[27] while protecting proteins against oxidative damage.[28]

If Dr. Budd's thinking (and results) had been more widely accepted when his publications appeared, thinking about "diabetes" might have led to earlier investigation of the syndromes of stress and tissue wasting, with insulin being identified as just one of many regulatory substances, and a large amount of useless and harmful activity treating hyperglycemia as the enemy, rather than part of an adaptive reaction, might have been avoided.

Glycemia, Starch, and Sugar in Context

Ray Peat's Newsletter, 2009

In the 1920s, "diabetes" was thought to be a disease of insulin deficiency. Eventually, measurements of insulin showed that "diabetics" often had normal amounts of insulin, or above-normal amounts. There are now "two kinds of diabetes," with suggestions that "the disease" will soon be further subdivided.

The degenerative diseases that are associated with hyperglycemia and commonly called diabetes, are only indirectly related to insulin, and as an approach to understanding or treating diabetes, the "glycemic index" of foods is useless. Physiologically, it has no constructive use, and very little meaning.

Insulin is important in the regulation of blood sugar, but its importance has been exaggerated because of the diabetes/insulin industry. Insulin itself has been found to account for only about 8 % of the "insulin-like activity" of the blood, with potassium being probably the largest factor. There probably isn't any process in the body that doesn't potentially affect blood sugar.

Glucagon, cortisol, adrenalin, growth hormone and thyroid tend to increase the blood sugar, but it is common to interpret hyperglycemia as "diabetes," without measuring any of these factors. Even when "insulin dependent diabetes" is diagnosed, it isn't customary to measure the insulin to see whether it is actually deficient, before writing a prescription for insulin. People resign themselves to a lifetime of insulin injections, without knowing why their blood sugar is high.

Insulin release is also stimulated by amino acids such as leucine, and insulin stimulates cells to absorb amino acids and to synthesize proteins. Since insulin lowers blood sugar as it disposes of amino acids, eating a large amount of protein without carbohydrate can cause a sharp decrease in blood sugar. This leads to the release of adrenalin and cortisol, which raise the blood sugar. Adrenalin causes fatty acids to be drawn into the blood from fat stores, especially if the liver's glycogen stores are depleted, and cortisol causes tissue protein to be broken down into amino acids, some of which are used in place of carbohydrate. Unsaturated fatty acids, adrenaline, and cortisol cause insulin resistance.

"Professional opinion" can be propagated about 10,000 times faster than research can evaluate it, or, as C. H. Spurgeon said, "A lie travels round the world while Truth is putting on her boots."

In the 1970s, dietitians began talking about the value of including "complex carbohydrates" in the diet. Many dietitians (all but one of the Registered Dietitians that I knew of) claimed that starches were more slowly absorbed than sugars, and so should be less disruptive to the blood sugar and insulin levels. People were told to eat whole grains and legumes, and to avoid fruit juices.

These recommendations, and their supporting ideology, are still rampant in the culture of the United States, fostered by the U.S. Department of Agriculture and the American Dietetic Association and the American Diabetes Association and innumerable university departments of home economics, dietetics, or nutrition.

Judging by present and past statements of the American Dietetic Association, I think some kind of institutional brain defect might account for their recommendations. Although the dietetic association now feebly acknowledges that sugars don't raise the blood sugar more quickly than starches do, they can't get away from their absurd old recommendations, which were never scientifically justified: "Eat more starches, such as bread, cereal, and starchy vegetables—6 servings a day or more. Start the day with cold (dry) cereal with nonfat/skim milk or a bagel with one teaspoon of jelly/jam. Put starch center stage—pasta with tomato sauce, baked potato with chili, rice and stir-fried beef and vegetables. Add cooked black beans, corn, or garbanzo beans (chickpeas) to salads or casseroles."

The Dietetic Association's association with General Mills, the breakfast cereal empire, (and Kellog, Nabisco, and many other food industry giants) might have something to do with their starchy opinions. Starch-grain embolisms can cause brain damage, but major money can also make people say stupid things.

In an old experiment, a rat was tube-fed ten grams of corn-starch paste, and then anesthetized. Ten minutes after the massive tube feeding, the professor told the students to find how far the starch had moved along the alimentary canal. No trace of the white paste could be found, demonstrating the speed with which starch can be digested and absorbed. The very rapid rise of blood sugar stimulates massive release of insulin, and rapidly converts much of the carbohydrate into fat.

It was this sort of experiment that led to the concept of "glycemic index," that ranks foods according to their ability to raise the blood sugar. David Jenkins, in 1981, knew enough about the old studies of starch digestion to realize that the dietitians had created a dangerous cult around the "complex carbohydrates," and he did a series of measurements that showed that starch is more "glycemic" than sucrose. But he simply used the amount of increase in blood glucose during the first two hours after ingesting the food sample, compared to that following ingestion of pure glucose, for the comparison, neglecting the physiologically complex facts, all of the processes involved in causing a certain amount of glucose to be present in the blood during a certain time. (Even the taste of sweetness, without swallowing anything, can stimulate the release of glucagon, which raises blood sugar.)

More important than the physiological vacuity of a simple glycemic measurement was the ideology within which the whole issue developed, namely, the idea that diabetes (conceived as chronic hyperglycemia) is caused by eating too much sugar, i.e., chronic hyperglycemia the illness is caused by the recurrent hyperglycemia of sugar gluttony. The experiments of Bernardo Houssay (1947 Nobel laureate) in the 1940s, in which sugar and coconut oil protected against diabetes, followed by Randle's demonstration of the antagonism between fats and glucose assimilation, and the growing recognition that polyunsaturated fatty acids cause insulin resistance and damage the pancreas, have made it clear that the dietetic obsession with sugar in relation to diabetes has been a dangerous diversion that has retarded the understanding of degenerative metabolic diseases.

Starting with the insulin industry, a culture of diabetes and sugar has been fabulized and expanded and modified as new commercial industries found ways to profit from it. Seed oils, fish oils, breakfast cereals, soybean products, and other things that were never eaten by any animal in millions of years of evolution have become commonplace as "foods," even as "health foods."

Although many things condition the rate at which blood sugar rises after eating carbohydrates, and affect the way in which blood glucose is metabolized, making the idea of a "glycemic index" highly misleading, it is true that blood sugar and insulin responses to different foods have some meaningful effects on physiology and health.

Starch and glucose efficiently stimulate insulin secretion, and that accelerates the disposition of glucose, activating its conversion to glycogen and fat, as well as its oxidation. Fructose inhibits the stimulation of insulin by glucose, so this means that eating ordinary sugar, sucrose (a disaccharide, consisting of glucose and fructose), in place of starch, will reduce the tendency to store fat. Eating "complex carbohydrates," rather than sugars, is a reasonable way to promote obesity. Eating starch, by increasing insulin and lowering the blood sugar, stimulates the appetite, causing a person to eat more, so the effect on fat production becomes much larger than when equal amounts of sugar and starch are eaten. The obesity itself then becomes an additional physiological factor; the fat cells create something analogous to an inflammatory state. There isn't anything wrong with a high carbohydrate diet, and even a high starch diet isn't necessarily incompatible with good health, but when better foods are available they should be used instead of starches. For example, fruits have many advantages over grains, besides the difference between sugar and starch. Bread and pasta consumption are strongly associated with the occurrence of diabetes, fruit consumption has a strong inverse association.

Although pure fructose and sucrose produce less glycemia than glucose and starch do, the different effects of fruits and grains on the health can't be reduced to their effects on blood sugar.

Orange juice and sucrose have a lower glycemic index than starch or whole wheat or white bread, but it is common for dietitians to argue against the use of orange juice, because its index is the same as that of Coca-Cola. But, if the glycemic index is very important, to be rational they would have to argue that Coke or orange juice should be substituted for white bread.

After decades of "education" to promote eating starchy foods, obesity is a bigger problem than ever, and more people are dying of diabetes than previously. The age-specific incidence of most cancers is increasing, too, and there is evidence that starch, such as pasta, contributes to breast cancer, and possibly other types of cancer.

The epidemiology would appear to suggest that complex carbohydrates cause diabetes, heart disease, and cancer. If the glycemic index is viewed in terms of the theory that hyperglycemia, by way of "glucotoxicity," causes the destruction of proteins by glycation, which is seen in diabetes and old age, that might seem simple and obvious.

Glycemic List	White Bread	Glucose Based
Fructose	32	22
Lactose	65	46
Honey	83	58
High fructose corn syrup	89	62
Sucrose	92	64
Glucose	137	96
Glucose tablets	146	102
Maltodextrin	150	105
Maltose	150	105
Pineapple juice	66	46
Peach, canned	67	47
Grapefruit juice	69	48
Orange juice	74	52
Barley flour bread	95	67
Wheat bread, high fiber	97	68
Wheat bread, wholemeal flour	99	69
Melba toast	100	70
Wheat bread, white	101	71
Bagel, white	103	72
Kaiser rolls	104	73
Whole-wheat snack bread	105	74
Bread stuffing	106	74
Wheat bread, Wonderwhite	112	78
Wheat bread, gluten free	129	90
French baguette	136	95
Taco shells	97	68
Cornmeal	98	69
Millet	101	71
Rice, Pelde	109	76
Rice, Sunbrown Quick	114	80
Tapioca, boiled with milk	115	81
Rice, Calrose	124	87
Rice, parboiled, low amylose Pelde	124	87
Rice, white, low amylose	126	88
Rice, instant, boiled 6 min	128	90

But there are many reasons to question that theory.

Oxidation of sugar is metabolically efficient in many ways, including sparing oxygen consumption. It produces more carbon dioxide than oxidizing fat does, and carbon dioxide has many protective functions, including increasing Krebs cycle activity and inhibiting toxic damage to proteins. The glycation of proteins occurs under stress, when less carbon dioxide is being produced, and the proteins are normally protected by carbon dioxide.

When sugar (or starch) is turned into fat, the fats will be either saturated, or in the series derived from omega-9 monounsaturated fatty acids. When sugar isn't available in the diet, stored glycogen will provide some glucose (usually for a few hours, up to a day), but as that is depleted, protein will be metabolized to provide sugar. If protein is eaten without carbohydrate, it will stimulate insulin secretion, lowering blood sugar and activating the stress response, leading to the secretion of adrenalin, cortisol, growth hormone, prolactin, and other hormones. The adrenalin will mobilize glycogen from the liver, and (along with other hormones) will mobilize fatty acids, mainly from fat cells. Cortisol will activate the conversion of protein to amino acids, and then to fat and sugar, for use as energy. (If the diet doesn't contain enough protein to maintain the essential organs, especially the heart, lungs, and brain, they are supplied with protein from the skeletal muscles. Because of the amino acid composition of the muscle proteins, their destruction stimulates the formation of additional cortisol, to accelerate the movement of amino acids from the less important tissues to the essential ones.)

The diabetic condition is similar in many ways to stress, inflammation, and aging, for example in the chronic elevation of free fatty acids, and in various mediators of inflammation, such as tumor necrosis factor (TNF).

Rather than the sustained hyperglycemia which is measured for determining the glycemic index, I think the "diabetogenic" or "carcinogenic" action of starch has to do with the stress reaction that follows the intense stimulation of insulin release. This is most easily seen after a large amount of protein is eaten. Insulin is secreted in response to the amino acids, and besides stimulating cells to take up the amino acids and convert them into protein, the insulin also lowers the blood sugar. This decrease in blood sugar stimulates the formation of many hormones, including cortisol, and under the influence of cortisol both sugar and fat are produced by the breakdown of proteins, including those already

forming the tissues of the body. At the same time, adrenalin and several other hormones are causing free fatty acids to appear in the blood.

Since the work of Cushing and Houssay, it has been understood that blood sugar is controlled by antagonistic hormones: Remove the pituitary along with the pancreas, and the lack of insulin doesn't cause hyperglycemia. If something increases cortisol a little, the body can maintain normal blood sugar by secreting more insulin, but that tends to increase cortisol production. A certain degree of glycemia is produced by a particular balance between opposing hormones.

Tryptophan, from dietary protein or from the catabolism of muscles, is turned into serotonin which activates the pituitary stress hormones, increasing cortisol, and intensifying catabolism, which releases more tryptophan. It suppresses thyroid function, which leads to an increased need for the stress hormones. Serotonin impairs glucose oxidation, and contributes to many of the problems associated with diabetes.

"Diabetes" is often the diagnosis, when excess cortisol is the problem. The hormones have traditionally not been measured before diagnosing diabetes and prescribing insulin or other chemical to lower the blood sugar. Some of the worst effects of "diabetes," including retinal damage, are caused or exacerbated by insulin itself.

Antiserotonin drugs can sometimes alleviate stress and normalize blood sugar. Simply eating sucrose was recently discovered to restrain the stress hormone system.[1]

The free fatty acids released by the stress hormones serve as supplemental fuel, and increase the consumption of oxygen and the production of heat. (This increased oxygen demand is a problem for the heart when it is forced to oxidize fatty acids.[2]) But if the stored fats happen to be polyunsaturated, they damage the blood vessels and the mitochondria, suppress thyroid function, and cause "glycation" of proteins. They also damage the pancreas, and impair insulin secretion.

A repeated small stress, or overstimulation of insulin secretion, gradually tends to become amplified by the effects of tryptophan and the polyunsaturated fatty acids, with these fats increasing the formation of serotonin, and serotonin increasing the liberation of the fats.

The name, "glycation," indicates the addition of sugar groups to proteins, such as occurs in diabetes and old age, but when tested in a controlled experiment, lipid peroxidation of polyunsaturated fatty acids produces the protein damage about 23 times faster than the simple

sugars do.[3] And the oxidation of fats rather than glucose means that the proteins won't have as much protective carbon dioxide combined with their reactive nitrogen atoms, so the real difference in the organism is likely to be greater than that seen by Fu, et al.

These products of lipid peroxidation, HNE, MDA, acrolein, glyoxal, and other highly reactive aldehydes, damage the mitochondria, reducing the ability to oxidize sugar, and to produce energy and protective carbon dioxide.

Fish oil, which is extremely unstable in the presence of oxygen and metals such as iron, produces some of these dangerous products very rapidly. The polyunsaturated "essential fatty acids" and their products, arachidonic acid and many of the prostaglandin-like materials, also produce them.

When glucose can't be oxidized, for any reason, there is a stress reaction, that mobiles free fatty acids. Drugs that oppose the hormones (such as adrenalin or growth hormone) that liberate free fatty acids have been used to treat diabetes, because lowering free fatty acids can restore glucose oxidation.

Brief exposures to polyunsaturated fatty acids can damage the insulin-secreting cells of the pancreas, and the mitochondria in which oxidative energy production takes place. Prolonged exposure causes progressive damage. Acutely, the free polyunsaturated fatty acids cause capillary permeability to increase, and this can be detected at the beginning of "insulin resistance" or "diabetes." After chronic exposure, the leakiness increases and albumin occurs in the urine, as proteins leak out of the blood vessels. The retina and brain and other organs are damaged by the leaking capillaries.

The blood vessels and other tissues are also damaged by the chronically increased cortisol, and at least in some tissues (the immune system is most sensitive to the interaction) the polyunsaturated fats increase the ability of cortisol to kill the cells.

When cells are stressed, they are likely to waste glucose in two ways, turning some of it into lactic acid, and turning some into fatty acids, even while fats are being oxidized, in place of the sugar that is available. Growth hormone and adrenalin, the stress-induced hormones, stimulate the oxidation of fatty acids, as well as their liberation from storage, so the correction of energy metabolism requires the minimization of the stress

hormones, and of the free fatty acids. Prolactin, ACTH, and estrogen also cause the shift of metabolism toward the fatty acids.

Sugar and thyroid hormone (T_3, triiodothyronine) correct many parts of the problem. The conversion of T_4 into the active T_3 requires glucose, and in diabetes, cells are deprived of glucose. Logically, all diabetics would be functionally hypothyroid. Providing T_3 and sugar tends to shift energy metabolism away from the oxidation of fats, back to the oxidation of sugar.

Niacinamide, used in moderate doses, can safely help to restrain the excessive production of free fatty acids, and also helps to limit the wasteful conversion of glucose into fat. There is evidence that diabetics are chronically deficient in niacin. Excess fatty acids in the blood probably divert tryptophan from niacin synthesis into serotonin synthesis.

Sodium, which is lost in hypothyroidism and diabetes, increases cellular energy. Diuretics, that cause loss of sodium, can cause apparent diabetes, with increased glucose and fats in the blood. Thyroid, sodium, and glucose work very closely together to maintain cellular energy and stability.

In Houssay's experiments, sugar, protein, and coconut oil protected mice against developing diabetes. The saturated fats of coconut oil are similar to those we synthesize ourselves from sugar. Saturated fats, and the polyunsaturated fats synthesized by plants, have very different effects on many important physiological processes. In every case I know about, the vegetable polyunsaturated fats have harmful effects on our physiology.

For example, they bind to the "receptor" proteins for cortisol, progesterone, and estrogen, and to all of the major proteins related to thyroid function, and to the vesicles that take up nerve transmitter substances, such as glutamic acid.

They allow glutamic acid to injure and kill cells through excessive stimulation; this process is similar to the nerve damage done by cobra venom, and other toxins.

Excess cortisol makes nerve cells more sensitive to excitotoxicity, but the cells are protected if they are provided with an unusually large amount of glucose.

The cells of the thymus gland are very sensitive to damage by stress or cortisol, but they too can be rescued by giving them enough extra glucose to compensate for the cortisol. Polyunsaturated fatty acids have

the opposite effect, sensitizing the thymus cells to cortisol. This partly accounts for the immunosuppressive effects of the polyunsaturated fats. (AIDS patients have increased cortisol and polyunsaturated fatty acids in their blood.[4])

Unsaturated fatty acids activate the stress hormones, sugar restrains them.

Simply making animals "deficient" in the unsaturated vegetable oils (which allows them to synthesize their own series of animal polyunsaturated fats, which are very stable), protects them against "autoimmune" diabetes, and against a variety of other "immunological" challenges. The "essential fatty acid" deficiency increases the oxidation of glucose, as it increases the metabolic rate generally.

Saturated fats improve the insulin-secreting response to glucose.

The protective effects of sugar, and the harmful effects of excessive fat metabolism, are now being widely recognized, in every field of physiology. The unsaturated vegetable fats, linoleic and linolenic acid and their derivatives, such as arachidonic acid and the long chain fish oils, have excitatory, stress promoting effects, that shift metabolism away from the oxidation of glucose, and finally destroy the respiratory metabolism altogether. Since cell injury and death generally involve an imbalance between excitation and the ability to produce energy, it is significant that the oxidation of unsaturated fatty acids seems to consume energy, lowering cellular ATP.[5]

The bulk of the age-related tissue damage classified as "glycation end-products" (or "advanced glycation end-products," AGE) is produced by decomposition of the polyunsaturated fats, rather than by sugars, and this would be minimized by the protective oxidation of glucose to carbon dioxide.

Protein of the right kind, in the right amount, is essential for reducing stress. Gelatin, with its antiinflammatory amino acid balance, helps to regulate fat metabolism.

Aspirin's antiinflammatory actions are generally important when the polyunsaturated fats are producing inflammatory and degenerative changes, and aspirin prevents many of the problems associated with diabetes, reducing vascular leakiness. It improves mitochondrial respiration[6] and helps to regulate blood sugar and lipids.[7] Aspirin's broad range of beneficial effects is probably analogous to vitamin E's, being

proportional to protection against the broad range of toxic effects of the polyunsaturated "essential" fatty acids.

Growth Hormone

Hormone of Stress, Aging, & Death?

Ray Peat's Newsletter, 2013

RECENTLY I heard Robert Sapolsky interviewed, and he was describing the changes that prepare the body for short-term stress. He said the energy-mobilizing hormones, adrenalin and cortisol, increase, while the hormones that don't contribute to meeting the immediate problem, including the sex hormones and growth hormone, are suppressed, to save energy; growth and reproductive processes can be suspended for the few minutes of acute stress, to make the body more able to meet its acute needs. He reiterated: Growth hormone is suppressed by stress.

Sapolsky has done very interesting work on the suppression of testosterone by stress, and on the way in which brain cells are killed by prolonged exposure to glucocorticoids. He showed that if extra glucose is supplied, the brain cells can survive their exposure to cortisol. In the body, adrenalin and the glucocorticoids increase the availability of glucose.

In the radio interview, he didn't have time for much detail, but it seemed to me that he wasn't talking about the same growth hormone that I have been reading about, and trying to understand, for years. Since people have asked me to write about the current anti-aging uses of GH, and its use in the dairy industry, Sapolsky's statements made me decide to think about some of the issues around the hormone.[†]

The "growth hormone" was named long before it was actually found, and the substance with that name turns out to be involved in many processes other than growth. It is being given to cows to make them produce more milk, and it is being given to people with the purpose of making them lean and muscular, and with the hope of building stronger bones.

It isn't surprising that the Growth Hormone helps breasts develop and promotes milk production, since it is very similar to prolactin. GH

[†] If Sapolsky had been talking about just mice and rats, his statement would have been generally accurate. Adrenaline stimulates rat pituitary cells to secrete GH, and since both increase the amount of free circulating fatty acids, it could be that rats' GH is suppressed by a fatty acid excess.

and prolactin are members of a family of proteins that have diverged from each other in evolution, but they still have many overlapping effects.

When GH is treated as a drug, it is supposed to have a discrete identity, based on the sequence of its amino acids. But the natural hormone (disregarding the existence of a variety of closely related peptides with slightly different amino acid composition) varies with time, being chemically modified even before it is secreted. For example, its acidic amino acids may be methylated, and its lysine groups may combine with sugars or carbon dioxide. The history of the protein in the body determines its exact structure, and therefore its biological effects.

Male animals secrete GH in pulses, but females secrete it more steadily. This pattern of secretion "masculinizes" or "feminizes" the liver (and other organs), determining the pattern of enzyme activity. It would be possible (though very difficult) to arrange a system for delivering doses in a pulsed, intermittent manner. In cows, this apparently isn't necessary, since the purpose of the growth hormone is presumably to "feminize" the milk-producing system. But the normal pattern of secretion is much more complex than simply being "pulsed" or "continuous," since it, like prolactin secretion, is responsive to changes in thyroid, estrogen, diet, stress, and many other factors.For example, hormones in this family are, as far back in evolution as they have been studied, involved in the regulation of water and minerals. It is well established that increased water (hypotonicity) stimulates prolactin, and increased sodium inhibits its secretion. Growth hormone is also closely involved with the regulation of water and salts.

One of the best known metabolic effects of GH is that, like adrenalin, it mobilizes fatty acids from storage. GH is known to antagonize insulin, and one of the ways it does this is simply by the ability of increased free fatty acids to block the oxidation of glucose. At puberty, the increased GH creates a mild degree of diabetes-like insulin resistance, which tends to increase progressively with age.

In his book, *Why Zebras Don't Get Ulcers*, Sapolsky acknowledges some situations in which GH is increased by stress in humans, but I think he misses the real ways in which it operates in stress. One of the interesting features of cortisol, which Sapolsky showed killed brain cells by making them unable to use glucose efficiently, is that it makes cells take up unsaturated fatty acids more easily, interfering with their energy production. Since growth hormone also has this kind of "diatebetogenic"

action, it might be desirable to suppress its secretion during stress, but in fact, there are several kinds of stress that clearly increase its secretion, and in animals as different as fish, frogs, cows, and people it can be seen to play roles in water and salt regulation, growth and development, stress, and starvation.

Heat, hypoglycemia, running, and some types of shock are known to stimulate growth hormone secretion, sometimes to levels ten or twenty times higher than normal. (Two kinds of stress that usually don't increase GH are cold and stimulus-deprivation.) I consider the growth hormone to be, almost as much as prolactin, a stress-inducible hormone. That's why I reasoned that, if an endocrinologist as good as Sapolsky can misunderstand GH to that degree, the public is even more likely to misunderstand the nature of the material, and to believe that it somehow acts just on muscle, fat, and bones.

And the normally functioning pituitary appears to be unnecessary to grow to normal height.[1]

W. D. Denckla discovered that the pituitary hormones are in some way able to accelerate the process of aging. They block the actions of thyroid hormone, decreasing the ability to consume oxygen and produce energy. The diabetes-like state that sets in at puberty involves the relative inability to metabolize glucose, which is an oxygen-efficient energy source, and a shift to fat oxidation, in which more free radicals are produced, and in which mitochondrial function is depressed. Diabetics, even though it is supposedly an inability of their cells to absorb glucose that defines their disease, habitually waste glucose, producing lactic acid even when they aren't "stressed" or exerting themselves enough to account for this seemingly anaerobic metabolism. It was noticing phenomena of this sort, occurring in a great variety of animal species, in different phyla, that led Denckla to search for what he called DECO (decreasing consumption of oxygen) or "the death hormone." (Vladimir Dilman noticed a similar cluster of events, but he consistently interpreted everything in terms of a great genetic program, and he offered no solution beyond a mechanistic treatment of the symptoms.)

Simply increasing the amount of free fatty acids in the blood will act like DECO or "the death hormone," but growth hormone has more specific metabolic effects than simply increasing our cells' exposure to fatty acids. The hormone creates a bias toward oxidizing of the most

unsaturated fatty acids (Clejan and Schulz), in a process that appears to specifically waste energy.

Growth hormone plays an important role in puberty, influencing ovarian function, for example.

Removing animals' pituitaries, Denckla found that their aging was drastically slowed. He tried to isolate the death hormone from pituitary extracts. He concluded that it wasn't prolactin, although prolactin had some of its properties. In the last publication of his that I know of on that subject, he reported that he was unable to isolate the death hormone, but that it was "in the prolactin fraction." Since rats have at least 14 different peptides in their prolactin family, not counting the multitude of modifications that can occur depending on the exact conditions of secretion, it isn't surprising that isolating a single factor with exactly the properties of the chronically functioning aging pituitary hasn't been successful.

Denckla's experiments are reminiscent of many others that have identified changes in pituitary function as driving forces in aging and degenerative diseases.

Menopause, for example, is the result of overactivity of the pituitary gonatropins, resulting from the cumulatively toxic effects of estrogen in the hypothalamus.

A. V. Everitt, in his book on the hypothalamus and pituitary in aging, reported on studies in which estrogen caused connective tissues to lose their elasticity, and in which progesterone seemed to be an antiestrogenic longevity factor. Later, he did a series of experiments that were very similar to Denckla's, in which removal of the pituitary slowed the aging process. Several of his experiments strongly pointed to the prolactin-growth hormone family as the aging factors. Removal of the pituitary caused retardation of aging similar to food restriction. These pituitary hormones, especially prolactin, are very responsive to food intake, and the growth hormone is involved in the connective tissue and kidney changes that occur in diabetes and aging.

A mutant dwarf mouse, called "little," has only 5 % to 10 % as much growth hormone as normal mice, and it has an abnormally long lifespan.

Many experiments show that prolactin and estrogen have synergistic effects in causing tissue degeneration, including cancerization, and that their effects tend to operate with fewer protective restraining influences in old age. Estrogen stimulates both prolactin and growth hormone

secretion. Thirty years ago, people were warning that estrogen contraceptives might produce diabetes, because they caused chronic elevation of growth hormone and free fatty acids.

Since estrogen causes a slight tendency to retain water while losing sodium, producing hypotonic body fluids, and since hypotonicity is a sufficient stimulus to cause prolactin secretion, I have proposed that it is estrogen's effect on the body fluids which causes it to stimulate prolactin. In pregnancy, the fetus is exposed to fluids more hypotonic than can be accounted for by estrogen and prolactin alone; since GH lowers the salt concentration of fish when they enter the ocean from freshwater, it seems to be a candidate for this effect in pregnancy.

Growth itself is an intrinsic property of all cells, but the growth hormone does have its greatest influence on certain tissues, especially cartilage. Gigantism and acromegaly were what originally made people interested in looking for a growth hormone, and these are characterized by continued, exaggerated enlargement of bones and cartilage. In old age, cartilaginous structures such as the bones and ears keep enlarging. The fact that simply diluting the culture medium is sufficient to stimulate the growth of cartilage suggests that the growth hormone might be acting by its effects on water metabolism. In fish which enter fresh water from the ocean, pituitary hormones of this family help them to balance salts in this new environment, but in the process, they develop osteoporosis and skeletal deformity, of the sort that occur more gradually in other animals with aging.

Growth hormone clearly causes edema, and this is probably involved in the pathological processes that it can produce. The expansion of extracellular water has been reported, but others have concluded that the increased weight of muscles following GH treatment must be the result of "growth," "because microscopic examination didn't show edema." Statements of that sort give incompetence a bad name, because any student of biology or biochemistry has to know, before he does almost any experiment, that the way to determine the water content of a tissue is to compare the wet weight to the weight after thorough drying. Looking for water under a microscope is the sort of thing they do at drug companies to pretend that they have done something.

Estrogen, growth hormone, and nitric oxide, which tend to work as a system, along with free fatty acids, all increase the permeability of blood vessels. The leaking of albumin into the urine, which is characteristic

of diabetes, is promoted by GH. In diabetes and GH treatment, the basement membrane, the jelly-like material that forms a foundation for capillary cells, is thickened. The reason for this isn't known, but it could be a compensatory "anti-leak" response tending to reduce the leakage of proteins and fats.

Besides being involved in kidney degeneration, vascular leakiness contributes to brain edema, and probably contributes to the "autoimmune" diseases.

Whatever the exact mechanism may be, it is clearly established that GH contributes to kidney degereration, and the lack of GH, even the removal of the pituitary, is protective against kidney degeneration.

Denckla's and Everitt's experiments can be interpreted much more clearly now that GH's essential contribution to kidney degeneration is known. Growth Hormone may not be precisely the Death Hormone that Denckla was looking for, but it is very close to it. Anti-thyroid effects have been seen, and possibly even anti-growth effects during gestation, and in kidney disease. In newborns, high GH is associated with smaller size and slower growth; in one study, this was associated with rapid breathing, presumably hyperventilation which is associated with stress. The shift to the diabetes-like fatty acid oxidation would be expected to inhibit respiration, and the chronic elevation of serum free fatty acids will have a generalized antithyroid effect. Under the influence of GH, the proportion of unsaturated fatty acids is increased, as occurs under the influence of estrogen.

Growth hormone blocks gonadotropin-stimulated progesterone production, and this could also affect thyroid and respiratory metabolism.

The increase of GH during sleep might seem to be utterly incompatible with the idea that it is a stress hormone, but in fact the other stress hormones, adrenalin, cortisol, and prolactin also tend to increase during night-time sleep. Thyroid function and progesterone function decrease at night. As I have argued previously darkness is one of our major stressors. Considering GH's tendency to cause edema, tissue swelling, it could play a role in the nocturnal increase of the viscosity of blood, as the volume of blood is decreased by the leakage of fluid into the tissues. Another process with potentially deadly results that increase with aging and stress, is the passage of bacteria from the intestine into the blood stream; this process is increased under the influence of GH.

Acute, short term studies definitely show growth hormone to be a stress hormone with some destabilizing effects. Over a lifetime, it is possible that such things as chronically increased levels of unsaturated fatty acids in the blood, and increased leakiness of the blood vessels, could cumulatively produce the effects that Denckla ascribed to the Death Hormone.

Heart and Hormones

Ray Peat's Newsletter, 2015

THE drug industry has been lowering the numbers for cholesterol, blood pressure, and blood glucose that are considered to be the upper limit of normal, increasing the number of customers for their prescription drugs. Recently, publications have been claiming that the upper limit of the normal range of heart rates should be lower than 100 beats per minute; this would encourage doctors to prescribe more drugs to slow hearts, but the way the evidence is being presented, invoking the discredited "wear and tear" theory of aging, could have many unexpected harmful consequences. It would reinforce existing misconceptions about heart functions.

A few decades ago, diuretics to lower blood pressure and digitalis/digoxin to increase the heart's strength of contraction were the main treatments for heart disease. In 1968, the annual number of deaths in the U.S. from congestive heart failure (in which the heart beats more weakly, pumping less blood) was 10,000. By 1993 the number had increased to 42,000 per year. More recently, the annual number of deaths in which heart failure is the primary cause was more than 55,000. During these decades, many new drugs for treating heart disease were introduced, and the use of digoxin has decreased slightly. People with heart failure usually live with the condition for several years; at present about 5.7 million people in the U.S. live with heart failure. The prevalence of, and mortality from, other cardiovascular diseases (such as hypertension and abnormalities of the coronary arteries) are higher, but congestive heart failure is especially important to understand, because it involves defective function of the heart muscle itself.

Although Albert Szent-Györgyi is known mostly for his discovery of vitamin C and his contribution to understanding the tricarboxylic acid or Krebs cycle, his main interest was in understanding the nature of life itself, and he focused mainly on muscle contraction and cancer growth regulation. In one of his experiments, he compared the effects of estrogen and progesterone on rabbit hearts. A basic property of the heart muscle is that when it beats more frequently, it beats more strongly. This is called the staircase effect, from the way a tracing of its motion rises, beat by beat, as the rate of stimulation is increased. This is a logical

way to behave, but sometimes it fails to occur: In shock, and in heart failure, the pulse rate increases, without increasing the volume of blood pumped in each contraction.

Szent-Györgyi found that estrogen treatment decreased the staircase effect, while progesterone treatment increased the staircase. He described the staircase as a situation in which function (the rate of contraction) builds structure (the size of the contraction). Progesterone allowed "structure" to be built by the contraction, and estrogen prevented that.

(It's interesting to compare these effects of the hormones to the more general idea of anabolic and catabolic hormones, in which more permanent structures in cells are affected.)

The rapid and extensive alternation of contraction and relaxation made possible by progesterone is also produced by testosterone.[1] Things that increase the force of contraction are called inotropic, and the things that promote relaxation are called lusitropic; progesterone and testosterone are both positively inotropic and lusitropic, improving contraction and relaxation. Estrogen is a negative lusitropic hormone,[2] and also a negative inotropic hormone,[3] that is, it impairs both relaxation and contraction.

Another standard term describing heart function is chronotropy, referring to the frequency of contraction. Because of the staircase interaction of frequency and force, there has been some confusion in classifying drugs according to chronotropism. In a state of shock or estrogen dominance, an inotropic drug will slow the heart rate by increasing the amount of blood pumped. This relationship caused digitalis' effect to be thought of as primarily slowing the rate of contraction,[4] though its main effect is positively inotropic. It was traditionally used to treat edema, by stimulating diuresis, which is largely the result of its inotropic action. Progesterone and testosterone's inotropic action can also slow the heart beat by strengthening it.

I think it was a little before Szent-Györgyi's heart experiment that Hans Selye had discovered that a large dose of estrogen created a shock-like state. Shock and stress cause estrogen to increase, and decrease progesterone and testosterone.

About 30 years after Szent-Györgyi's work, people began to realize that digoxin and other heart stimulating molecules can be found

in animals and humans, as metabolites of progesterone and possibly DHEA.[5]

The regulatory proteins that are involved in estrogen's negative lusi- and inotropic actions (decreasing pumping action) have been known for over 20 years to be regulated by the thyroid hormone to produce positive lusi- and inotropic actions on the heart (increasing its pumping action), and thyroid's beneficial effects on heart and skeletal muscle have been known empirically for 100 years. However, drug centered cardiologists, reviewing the currently available drugs approved by the FDA, have typically concluded that "drugs targeted to achieve these objectives are not available."[6]

When a muscle or nerve is fatigued, it swells, retaining water. When the swelling is extreme, its ability to contract is limited. Excess water content resembles a partly excited state, in which increased amounts of sodium and calcium are free in the cytoplasm. Energy is needed to eliminate the sodium and calcium, or to bind calcium, allowing the cell to extrude excess water and return to the resting state. Thyroid hormone allows cells' mitochondria to efficiently produce energy, and it also regulates the synthesis of the proteins (phospholamban and calcisequestrin) that control the binding of calcium. When the cell is energized, by the mitochondria working with thyroid, oxygen, and sugar, these proteins rapidly change their form, binding calcium and removing it from the contractile system, allowing the cell to relax, to be fully prepared for the next contraction. If the calcium isn't fully and quickly bound, the cell retains extra water and sodium, and isn't able to fully relax.

Heart failure is described as "diastolic failure" when the muscle isn't able to fully relax. In an early stage, this is just a waterlogged,[7] fatigued condition, but when continued, the metabolic changes lead to fibrosis and even to calcification of the heart muscle.

Many children approaching puberty, as estrogen is increasing and interfering with thyroid function, have "growing pains," in which muscles become tense and sore after prolonged activity. When hypothyroidism is severe, it can cause myopathy, in which the painful swollen condition involves the leakage of muscle proteins (especially myoglobin) into the blood stream, allowing it to be diagnosed by a blood test. The combination of hypothyroidism with fatigue and stress can lead to the breakdown and death of muscle cells, rhabdomyolysis.

The blood lipid lowering drugs, statins and fibrates, impair mitochondrial respiration,[8–10] and increase the incidence of rhabdomyolysis.[11–13] Interference with coenzyme Q_{10} is not the only mechanism by which they can cause myopathy.[14] The harmful effect of lowering cholesterol seems to be relevant to heart failure: "In light of the association between high cholesterol levels and improved survival in HF, statin or other lipid-lowering therapy in HF remains controversial."[15]

Heart muscle and skeletal muscle are similar in their structural responses to interference with mitochondrial functions, namely, swelling, reduced contractile ability, and dissolution. When myoglobin has been found in the blood and urine, it has been assumed to come from skeletal muscles, but the heart's myoglobin has been found to be depleted in a patient with myoglobinuria.[16] When heart failure is known to exist, similar changes can be found in the skeletal muscles.[17]

Stress, in the form of pressure-overload,[18] or overactivity of the renin-angiotensin system[19] and sympathetic nervous system or adrenergic chemicals,[20] or a failure of energy caused by diabetes, insulin deficiency, or hypothyroidism, causes a shift of energy production from the oxidation of glucose to the oxidation of fatty acids, with the release, rather than oxidation, of the lactic acid produced from glucose. This sequence, from reduced efficiency of energy production to heart failure, can be opposed by agents that reduce the availability of fatty acids and promote the oxidation of glucose. Niacinamide inhibits the release of free fatty acids from the tissues, and thyroid sustains the oxidation of glucose. This principle is now widely recognized, and the FDA has approved a drug that inhibits the oxidation of fatty acids,[21] but which has serious side effects. Glucose oxidation apparently is necessary for preventing the intracellular accumulation of free calcium and fatty acids.[22–24] The calcium binding protein which is activated by thyroid and inhibited by estrogen seems to be activated by glucose and inhibited by fatty acids.[25]

Diabetes or fasting increases free fatty acids, and forces cells to shift from oxidation of glucose to oxidation of fatty acids, inhibiting the binding of calcium.[26] Providing a small amount of sugar (0.8 % sucrose in their drinking water) restored the calcium binding and heart function, without increasing either thyroid hormone or insulin.[26–28] Serum glucose was lowered, as the ability to oxidize sugar was restored by lowering free fatty acids. Activity of the sympathetic nervous system is lowered as efficiency is increased.

Digoxin stimulates mitochondrial energy production in skeletal and heart muscle,[29] increasing the oxidation of glucose, rather than fatty acids, supporting the effect of thyroid hormone. The statins have the opposite effect, decreasing the oxidation of glucose.

One of estrogen's effects is to chronically increase the circulation of free fatty acids, and to favor the long chain polyunsaturated fatty acids, such as EPA and DHA. These fatty acids, which slow the heart rate,[30] extend the excited state (action potential[31]), and are negatively inotropic,[32–34] are being proposed as heart protective drugs. (EPA and alpha-linoleic acid also prolong the QT interval[32]).

Many publications still promote estrogen as a cardioprotective drug, but there is now increased recognition of its role in heart failure and sudden cardiac death. A prolonged excited state (action potential) and delayed relaxation (QT interval) are known to increase the risk of arrhythmia and sudden death, and estrogen, which causes those changes in humans, causes sudden cardiac death in susceptible rabbits, with an adrenergic stimulant increasing the arrhythmias, and progesterone and androgen preventing them.[35] Progesterone's protective effect seems to be the result of accelerating recovery of the resting state.[36]

Estrogen's interactions with adrenalin in promoting blood vessel constriction has been known for many years.[37] Progesterone blocks that effect of estrogen.[38] Environmental estrogens such as BPA can exacerbate ventricular arrhythmia caused by estrogen.[39] The hearts of mice genetically engineered to lack aromatase, the enzyme that synthesizes estrogen, were more resistant to damage by being deprived of blood for 25 min,[40] leading the authors to suggest that aromatase inhibition might be helpful for heart disease.

In the stressed, energy depleted failing heart, muscle cells die and are replaced by connective tissue cells. The growth produced by overexposure to adrenergic stimulation leads to stiffening and reduced functioning. However, under the influence of thyroid hormone a high work load leads to functional enlargement, which simply increases the pumping ability. Because of the traditional belief that heart cells can't replicate, this functional growth was believed to be produced purely by the enlargement of cells, but in recent years the existence of stem cells able to create new heart muscle has been recognized. Thyroid is likely to be one of the hormones responsible for allowing stem cells to differentiate into cardiomyocytes.

In this context, of cellular differentiation as a life-long process, we can see the changes of a failing heart as a differentiation which is forced to take an inappropriate course. The calcification of blood vessels caused by phosphate excess and vitamin K deficiency involves the expression of a protein which has its proper place in the skeleton. The replacement of heart muscle by fibrous connective tissue and even bone is a basic biological problem of differentiation, and the responsible factors—stress, increased estrogen, deficient thyroid hormone, suppression of glucose oxidation by fatty acids, etc.—are involved in the problems of differentiation that occur in other degenerative processes, such as sarcopenia, dementia, and cancer.

There have been arguments about the nature of wound healing and regeneration, regarding the origin of the new cells—whether they are from the dedifferentiation of local cells, or the migration of stem cells. The evidence is that both can occur, depending on the tissue and the situation. The deterioration of an organ is probably not a question of a lack of stem cells, but of changed conditions causing them to differentiate into something inappropriate for the full functioning of that organ.

Various stresses can cause cells to dedifferentiate, but hypoxia is probably a common denominator. In the absence of estrogen, hypoxia can activate the "estrogen receptor." Estrogen is in some situations a hormone of dedifferentiation, facilitating the formation of new cells in stressed tissues, as aromatase is induced. However, the presence of polyunsaturated fats, tending to increase in concentration with age, causes the processes of renewal to produce exaggerated inflammation, with prostaglandins participating in the processes of development and differentiation. Estrogen, by increasing the concentration of free fatty acids, especially polyunsaturated fatty acids, contributes to the metabolic shift away from glucose oxidation, toward the formation of lactic acid, and away from the full organ-specific differentiation.

This perspective puts heart failure, cancer, and the other degenerative diseases onto the same biological basis, and shows why certain conditions and therapies can be appropriate for all of them.

Problems that seem relatively trivial become more meaningful when they are seen in terms of these mechanisms. Some problems that become very common by middle age are "palpitations," orthostatic hypotension, orthostatic tachycardia, and varicose veins. The negative inotropic effect of estrogen in the heart has a parallel in the smooth muscle of veins,

in which the muscles are weakened, and their distensibility increased, when estrogen isn't sufficiently opposed by progesterone. This allows the veins in the lower part of the body to be distended abnormally when standing, reducing the amount of blood returning to the heart, so that the volume pumped with each stroke is small, requiring faster beating. The reduced blood volume reaching the brain can cause fainting. When it becomes chronic, it can lead to the progressive distortion of the veins. An excess of estrogen is associated with varicose veins in men, as well as women.[41–45]

The simplicity of things such as supplementing thyroid, progesterone, and sugar, avoiding an excess of phosphate in relation to calcium, and avoiding polyunsaturated fats, makes it possible for people to take action themselves, without having to depend on the medical system. Most physicians still warn their patients of the dangers of thyroid supplements, especially the active T_3 hormone, for their heart, but in at least one specialty, its value is recognized. Heart transplant surgeons have discovered that administering T_3 to the brain-dead heart donor before removing the heart improves its viability and function in the recipient.[46] Around this time, the manufacturers of Cytomel conceived the idea of marketing it as a "heart drug," which would make it much more profitable.

Another technique that is easy to use to lower blood pressure and improve heart rhythm is to breathe into a paper bag for a minute or two at a time, to increase the carbon dioxide content of the blood. This has a vasodilating effect, reducing the force required to circulate the blood, and reduces anxiety. Rhubarb and emodin (a chemical found in rhubarb and cascara) have been found to have heart protective actions. A considerable amount of research showed that vitamin K is effective for treating hypertension, but again, most doctors warn against its use, because of its reputation as a clot forming vitamin. Recently, the value of the "blood thinner" warfarin, a vitamin K antagonist, has been questioned for people with heart failure.[47,48] There have been several recent warnings about the production of arrhythmia by drugs that increase serotonin's effects.[49]

Measuring the speed of relaxation of the Achilles tendon reflex twitch is a traditional method for judging thyroid function, because in hypothyroidism the relaxation is visibly delayed. This same retardation can be seen in the electrocardiogram, as a prolonged QT interval, which

is associated with arrhythmia and sudden death. Insomnia, mania, and asthma are other conditions in which defective relaxation is seen, under the influence of low thyroid function, and an insufficiently opposed influence of estrogen.

Hot Flashes, Energy, and Aging

Ray Peat's Newsletter, 2013

Around the time that menstruation and fertility are ending, certain biological problems are more likely to occur. Between the ages of 50 and 55, about 60 % of women experience repeated episodes of flushing and sweating. Asthma, migraine, epilepsy, arthritis, varicose veins, aneurysms, urticaria, reduced lung function, hypertension, strokes, and interstitial colitis are some of the other problems that often begin or get worse at the menopause, but that normally aren't considered to be causally related to it.

Recently, hot flashes are being taken more seriously, because of their association with increased inflammation, heart disease, and risk of dementia. Around the same age, late 40s to mid-50s, men begin to have a sudden increase of some of the same health problems, including night sweats, anxiety, and insomnia. In both sexes, the high incidence of depression in this age group has usually been explained "psychologically," rather than biologically.

When the estrogen industry began concentrating on women of menopausal age (after the disastrous years of selling it as a fertility drug), "estrogen replacement" therapy was promoted as a cure for the problems associated with menopause, including hot flashes, which were explained as the result of a deficiency of estrogen. However, in recent years, the phrase "estrogen deficiency" has begun to be replaced by the phrase "estrogen withdrawal," because it has been found that women with hot flashes don't necessarily have less estrogen in their blood stream than women who don't have hot flashes.

Associated with this change of terminology, there has been a recognition that changes in the temperature regulating system in the brain, rather than changes in the amount of estrogen, are responsible for the hot flashes, but mainstream medicine has carefully avoided the investigation of this subject. The effects of estrogen on the thermoregulatory system are very clear, but the standard medical view is that the physiology of hot flashes simply isn't understood.

Since the medical literature boldly describes the mechanisms of the circulatory system and the causes of major problems such as heart

attacks, high blood pressure, and strokes, it's odd that it doesn't have an explanation for "hot flashes."

But looking at this historically, I think this selective ignorance is necessary, for the protection of some doctrines that have become very important for conventional medicine.

When doctors are talking about diseases of the heart and circulatory system, it's common for them to say that estrogen is protective, because it causes blood vessels to relax and dilate, improving circulation and preventing hypertension. The fact that estrogen increases the formation of nitric oxide, a vasodilator, is often mentioned as one of its beneficial effects. But in the case of hot flashes, dilation of the blood vessels is exactly the problem, and estrogen is commonly prescribed to prevent the episodic dilation of blood vessels that constitutes the hot flash. Nitric oxide increases in women in association with the menopause,[1] and it is increased by inflammation, and hot flushes are associated with various mediators of inflammation, but, as far as I can tell, no one has measured the production of nitric oxide during a hot flash. Inhibitors of nitric oxide formation reduce vasodilation during hot flushes.[2]

Starting in the 1940s, the doctrine that menopause is the result of changes in the ovaries, involving a depletion of eggs and an associated loss of estrogen production, was widely taught to medical students. By the 1970s, the taboo against discussing menopause publicly was fading, and the mass media began teaching the public that hot flashes are the result of an estrogen deficiency, and that "estrogen replacement" is the most appropriate and effective treatment, and in the next 20 years almost half the women in the U.S. began taking it around the time of menopause. This practice became routine at a time when "evidence based medicine" was being promoted as a new standard, but there was no evidence that women experiencing hot flashes were deficient in estrogen (in fact, there was evidence that they weren't), and there was evidence that hot flashes began when the first menstrual period was missed, which coincided with, and resulted from, a failure to produce a functional corpus luteum, preventing the production of a normal amount of progesterone. But the silly old doctrine of deficiency is often restated by professors, as if there was no doubt about it.[3]

This extremely persistent disregard for important evidence about the nature of menopause and its symptoms was guided by the estrogen industry, which began in the 1930s to call estrogen "the female hor-

mone," disregarding the facts about the biological roles of estrogen and progesterone, because chemicals with estrogenic effects were numerous and cheap, while progesterone was expensive, and had no synthetic equivalents. At the time the pharmaceutical industry began promoting estrogen as the female hormone to prevent miscarriage, it was already well known that it could produce abortion, as well as causing inflammation and cancer, and some of the most famous estrogen researchers were warning of its multiple dangers in the 1930s.

Menopause is a major landmark of aging, and if its meaning is radically misunderstood, a coherent understanding of aging is unlikely, and without an understanding of the loss of functions with age, we won't really understand life. More specifically, the real causes of the many serious problems occurring in association with the menopause will be ignored. Finding the causes of the seemingly trivial hot flash will affect the way we understand aging and its diseases.

If a common occurrence is thought to have some importance in itself, or to relate closely to something of importance, it will be described carefully, and its general features will become part of the common understanding. It's clear that our medical culture hasn't considered the hot flash to be important, because there are still physicians who believe that the hot flash represents a rise of body temperature caused by a sudden increase of heat production, which they sometimes explain as an upward fluctuation of thyroid gland activity. Measurement of body temperature before and during hot flashes has shown clearly that the internal temperature is lowered slightly by the hot flash, as heat is lost from the skin, as a result of vasodilation. Physiologists have been studying the differences in temperature regulation between men and women, and the effects of hormones on temperature regulation, for more than 70 years, but the medical profession in the United States showed almost no interest in the subject for about 50 years.

August Weismann's doctrine of "mortal soma, immortal germ line," led people to postulate that "primordial germ" cells migrated into the ovary (consisting of "somatic" cells) during embryonic development, and that the baby was born with a supply of germ cells that was used up during the reproductive lifetime, accounting for the decline of fertility with aging. The fact that menstrual cycles ended around the time that fertility ended was explained by the idea that ovulation caused the release of estrogen, and that the absence of eggs caused a failure to produce

estrogen, and that the absence of estrogen led to the failure of the cyclical uterine changes. It was all deduced from a mistaken ideology about the nature of life.

Cancer of the endometrium (lining) of the uterus and breast cancer were known to be the first and second cancers, respectively, produced by uninterrupted exposure to estrogen.[4] Investigation of the causes of endometrial cancer showed that women with anovulatory cycles, that failed to produce progesterone, or who had a reduced production of progesterone, developed overgrowth of the endometrium, and that these were the women who were later most likely to develop cancer of the endometrium. The peak incidence of endometrial cancer is in the postmenopausal years, resulting from prolonged exposure to estrogen, unopposed by progesterone. The medical belief† that "ovulation produces estrogen," and that the absence of menstruation means an absence of estrogen, has been very harmful to women's health.

Several laboratories, from the 1950s through the 1980s, investigated the causes of age-related infertility. A.L. Soderwall, among others, demonstrated that an excess of estrogen makes it impossible for the uterus to maintain a pregnancy.

Subsequently, his lab showed that neither changes in the eggs nor changes in the uterus could explain age related infertility. Altered pituitary hormone cycles, resulting from changes in the brain, could account for the major changes in the ovaries and uterus.

Other experimenters, including P.M. Wise, V.M. Sopelak and R.L.Butcher,[5] P.Ascheim,[6] and D.C.Desjardins[7] have clarified the interactions between the ovaries and the brain. For example, when the ovaries of an old animal are transplanted into a young animal, they are able to function in response to the new environment, but when the ovaries of a young animal are transplanted into an old animal, they fail to cycle. However, if the ovaries are removed from an animal when it's young, so that it lives to the normal age of infertility without being regularly exposed to surges of estrogen, it will then be able to support normal cycles when young ovaries are transplanted into it. But if it received estrogen supplements throughout its life, transplanted young ovaries will fail to cycle.

The work of Desjardins and others has demonstrated that free radicals generated by interactions of estrogen and iron with unsaturated fatty acids are responsible for damage to brain cells.[8] The damaged

inhibitory nerve cells allow the pituitary to remain in a chronically active state; in old rats, this can produce a state of constant estrus. Several groups[9–11] have shown that removal of the pituitary gland can greatly extend lifespan, if thyroid hormone is supplemented.

One of the animal "models" used to study hot flashes is morphine withdrawal. The model seems relevant to human hot flashes, because estrogen can stop the morphine withdrawal flushing, and estrogen's acute and chronic effects on the brain-pituitary-ovary system involve the endorphins and the opioidergic nerves.[12,13]

In young rats, sudden morphine withdrawal caused by injecting the anti-opiate naloxone, causes the tail skin to flush, with a temperature increase of a few degrees, and causes the core body temperature to fall slightly. However, old animals respond to the withdrawal in two different ways. One group responded to the naloxone with an exaggerated flushing and decrease of core temperature. The other group of old rats, which already had a lower body temperature, didn't flush at all.[14] I think this provides an insight into the reason that menopausal treatment with estrogen can relieve some hot flashes—estrogen treatment might create a flush resistant state similar to that of the cooler old animals in Simpkins' experiment.

It has been known for a long time, from studies in animals and people, that estrogen lowers body temperature, and that this involves a tendency to increase blood flow to the skin in response to a given environmental temperature, that is, the temperature "set-point" is lowered by estrogen. Besides increasing heat loss, estrogen decreases heat production. These physiological effects of estrogen can be seen in the normal menstrual cycle, with progesterone having the opposite effect of estrogen on metabolic rate, skin circulation, body temperature, and heat loss. This causes the familiar rise in temperature when ovulation occurs. Occasionally, young women will experience hot flashes during the luteal phase of their menstrual cycle because of insufficient progesterone production, or at menstruation, when the corpus luteus stops producing progesterone.

Estrogen increases the free fatty acids circulating in the blood, and this shifts metabolism away from oxidation of glucose to oxidation of fat, and it also reduces oxidative metabolism, for example by lowering thyroid function.[15] These changes are analogous to those of fasting, in which metabolism shifts to the oxidation of fatty acids for energy, causes

decreased body temperature, and in some animals leads to a state of torpor or hibernation.

Despite decreasing oxidative metabolism, estrogen stimulates the adrenal cortex, both directly and indirectly through the brain and pituitary, increasing the production of cortisol. Cortisol, by increasing protein turnover, can increase heat production, but this effect isn't necessarily sufficient to maintain a normal body temperature. It increases blood glucose, mainly by blocking its use for energy production, but the glucose is derived from the breakdown of muscle protein. It allows some glucose to be stored as fat. Sudden increases in the amount of glucose can lower adrenaline, and chronically excessive cortisol tends to suppress adrenaline. Cushing's syndrome (produced by excessive cortisol) commonly involves flushing and depression, both of which are likely to be related to the decreased action of adrenaline.

While the biological changes occurring at menopause and during hot flashes are very similar to some of the direct actions of estrogen, and although the menopause itself is the result of prolonged exposure to estrogen, very large doses of estrogen can, in many women (as well as in morphine addicted rats), stop the flushing. In some of the published animal experiments, effective doses of estrogen were about 2000 times normal, and in some human studies, the dose was 30 times normal. By blocking the production of heat, the estrogen treatments might be creating conditions similar to those in Simpkin's cooler old rats, which failed to flush during morphine withdrawal. Menopausal estrogen treatment is known to lower temperature.[16]

Since the Women's Health Initiative publicized the dangers of estrogen, there has been some interest in alternative treatments for hot flashes. Since a reduced production of progesterone has been associated with hot flushes for several decades, it isn't surprising that it is now being tested as an alternative to estrogen. Recently, 300 mg of oral progesterone was found to be effective for decreasing hot flashes, and a month after discontinuing it, the hot flushes were still less frequent than before using it.[17] Previously, transdermal progesterone was found to be effective.[18]

One of the things progesterone does is to stabilize blood sugar. In one experiment, hot flashes were found to be increased by lowering blood sugar, and decreased by moderately increasing blood sugar.[19]

Hypoglycemia increases the brain hormone, corticotropin release hormone, CRH,[20] which increases ACTH and cortisol. CRH causes va-

sodilation,[21] and is more active in the presence of estrogen. Menopausal women are more responsive to its effects, and those with the most severe hot flushes are the most responsive.[22]

The first reaction to a decrease of blood glucose, at least in healthy individuals, is to increase the activity of the sympathetic nervous system, with an increase of adrenaline, which causes the liver to release glucose from its glycogen stores. The effect of adrenaline on the liver is very quick, but adrenaline also acts on the brain, stimulating CRH, which causes the pituitary to secrete ACTH, which stimulates the adrenal cortex to release cortisol, which by various means causes blood sugar to increase, consequently causing the sympathetic nervous activity to decrease. Even when the liver's glycogen stores are adequate, the system cycles rhythmically, usually repeating about every 90 min throughout the day.

Sympathetic nervous activity typically causes vasoconstriction in the skin and extremities, reducing heat loss, but the small cycles in the system normally aren't noticed, except as small changes in alertness or appetite. With advancing age, most tissues become less sensitive to adrenaline and the sympathetic nervous stimulation, and the body relies increasingly on the production of cortisol to maintain blood glucose. Many of the changes occurring around the menopause, such as the rise of free fatty acids and decrease of glucose availability, increase the sensitivity of the CRH nerves, causing the fluctuations of the adrenergic system to cause larger increases of ACTH and cortisol. Estrogen is another factor that increases the sensitivity of the CRH nerves, and unsaturated fatty acids[23] and serotonin[24] are other factors stimulating it. Serotonin, like noradrenalin, rises with hypoglycemia,[25] and estrogen contributes to hypoglycemia, by impairing the counterregulatory system.[26]

With the reduced vasoconstrictive effects of the sympathetic nerves, and the increased activity of CRH, cyclic vasodilation under the influence of cortisol will become more noticeable. With the onset of menopause, and in proportion to the number and intensity of symptoms (on the Greene Climacteric Scale), the daily secretion of cortisol was increased.[27]

Once the ideologically based doctrine of menopause as estrogen deficiency is discarded, it's possible to see its features as clues to the ways in which "stress" contributes to the age-related degeneration of the various systems of the body—not just the reproductive system, but also the immune system, the nutritive, growth, and repair processes,

and the motivational, emotional, and cognitive processes of the nervous systems. The changes around menopause aren't the same for all women, but the ways in which they vary can be understood in terms of the basic biological principles of energy and adaptation that are universal.

Each type of cell and organ is subject to injury, and in some cases these injuries are cumulative. In the healthy liver, which stores glycogen, toxins can be inactivated, for example by combining with glucuronic acid, derived from the stored glucose. With injury, such as alcoholism combined with a diet containing polyunsaturated fats, the liver's detoxifying ability is reduced. Even at an early stage, before there is a significant amount of fibrosis, the reduced activity of the liver causes estrogen to accumulate in the body. Estrogen's valuable actions are, in health, exerted briefly, and then the synthesis of estrogen is stopped, and its excretion reduces its activity, but when the liver's function is impaired, estrogen's activity continues, causing further deterioration of liver function, as well as injury of nerves such as Desjardins described, and the systemic energy shifts and stress activations mentioned above.

Besides lowering the liver's detoxifying ability, stress, hypoglycemia, malnutrition, hypothyroidism, and aging can cause estrogen to be synthesized inappropriately and continuously. With aging, estrogen begins to be produced throughout the body—in fat, muscles, skin, bones, brain, liver, breast, uterus, etc. Polyunsaturated fats are a major factor in the induction and activation of the aromatase enzyme, which synthesizes estrogen.

Increased synthesis of estrogen, with aromatase, and decreased excretion of it, by the liver and kidneys, are only two of the processes that affect the influence of estrogen during aging. Cellular stress (chemical, mechanical, hypoxemic, hypoglycemic[28–32]) increases estrogen receptors (which activate CRH and the stress response). The presence of estrogen receptors means that estrogen will be bound inside cells, where it acts to modify those cells. Before estrogen can reach the liver to be inactivated, it must be released from cells. Ordinarily, the cyclic production of progesterone has that function, by destroying the estrogen-binding proteins. Progesterone also inhibits the aromatase which synthesizes estrogen, and shifts the activities of other enzymes, including sulfatases and dehydrogenates, in a comprehensive process of eliminating the presence and activity of estrogen. At menopause, when the ovary fails to produce the cyclic progesterone, all of these processes of estrogen

inactivation fail. In the absence of progesterone, cortisol becomes more active, increasing aromatase activity, which now becomes chronic and progressive. The decrease of progesterone causes many other changes, including the increased conversion of polyunsaturated fatty acids to prostaglandins, and the formation of nitric oxide, all of which contribute to the tendency to flush.

† The limits of the belief system or consciousness of U.S. medicine are nicely defined by the topics included in the Index Medicus, which was published from 1879 to 2004, by the Surgeon General's Office of the U.S. Army, the American Medical Association, and the National Library of Medicine, at different times. If you look up any important topic in physiology or biochemistry in an index of scientific publications such as Biological Abstracts or Chemical Abstracts, and then look for the same subject in the Index Medicus, you will find some startling differences—long delays and antagonistic attitudes. At first the discrepancies seem ludicrous and hard to account for, but I think they can be explained by recognizing that the editors of medical journals consider science to be their enemy.

How Do You Know?

Students, Patients, and Discovery

Ray Peat's Newsletter, 2007

> "For the real world has inexhaustible splendour, the real life is full of meaning and abundance, where we grasp it, it is full of miracles and glory."
>
> — N. Hartmann
>
> "I am myself plus my circumstances."
>
> — Jose Ortega y Gasset

KNOWLEDGE should be useful and provisional. I think comparing the doctor-patient relationship with the teacher-student relationship can be useful, and it might suggest ways that both of them could be made more productive, with implications for the nature of learning and knowing.

40 or 50 years ago, advocates of student-centered education were encouraged by the popularity of psychologist Carl Rogers' client centered therapy. Rogers was interested in what made some therapists successful, and he found that their personality and attitude, not their theories or techniques, accounted for their success. Successful therapists had three essential traits. They offered their clients acceptance or "unconditional positive regard" and empathic understanding, and they themselves were congruent, not presenting a facade of authority or esoteric knowledge. According to Rogers, "accurate diagnosis" and "specific treatment" didn't have anything to do with helping the client.

Some therapists thought Rogers' approach was impractical, others were sure it was foolish. Medically oriented psychiatrists saw Roger's prestige among psychologists as evidence that psychology wasn't suited for dealing with the "mentally ill," who needed authoritative diagnosis and treatment—such as drugs, convulsive shock, or surgery. Scientifically, however, Rogers' ideas were supported by evidence, and medical psychiatry had no evidence to support many of its diagnostic concepts or their therapeutic usefulness.

Most university professors felt that Rogers' ideas were irrelevant to their educational work, and some clearly saw their own function as being a sort of Malthusian selection of the fittest, and deliberately designed their classes as barriers that only a few could surmount.

When I taught English composition, instructors were told that they must grade according to a standard scoring system for errors of grammar, punctuation, spelling, and diction. Our success was seen in terms of the number of freshmen who had dropped out by the end of the year, as evidence that the department had "high standards." Knowing that system, most students chose to write in the style of the first grade "See Spot run" readers, hoping that they could handle the mechanics of writing if they reduced the complexity and content of their essays. It didn't work, and they didn't improve during the weeks when their mistakes were being brought painfully to their attention. Since I hated reading their meaningless efforts, I told them that I was going to grade them on content, rather than punctuation and spelling, and that they should try to write about something that was important to them. Only their success in communicating something would be graded. Their papers became more readable, and the interesting thing was that the mechanical things improved immediately. (The intention to communicate something is the real source of structure in language.) I had another teacher score some of their compositions, and he confirmed that they had improved according to the department's system. The attempt to steer a person can make it hard for them to move, because it inactivates their own guidance system.

A physics professor would notice that writing classes have a lot in common with psychotherapy, and would dismiss the possibility that such an approach could be used in serious education.

Professors of medicine see themselves as models of the authority that their students will need to apply in dealing with patients, and the physicians trained in the authoritarian style are likely to see their patients as recipients of their medical knowledge, rather than as occasions for listening and learning something new.

Students entering these disciplines must expect to be disciplined. This means that they learn not to ask silly questions about the fundamental assumptions of their profession. Their common sense of meaning, their original guidance system, must be inactivated to keep them from asking questions such as "is that a disease or a theory?" Some patients

find that their physician has little patience for their questions, but most patients don't want to ask questions, because they have been taught to respect the authorities.

Our nervous systems are made up of physiology and culture.

That can be a philosophical problem, because our experience is governed by our composition. In people like Heraclitus, physiology was in the foreground, and in people like Plato, culture was in the foreground. (Heraclitus understood that things are always becoming, Plato believed that change wasn't real.) To change someone's mind, it's necessary to change the way they experience themselves and the world, and that requires changing their substance.

In the 1950s a group called "Synectics" was formed to study the creative process. They found that having an expert in the group could be useful, but it could also often stifle the group's ability to find a good solution to a problem. W.J.J. Gordon described their method as "trusting things that are alien, and alienating things that are trusted." They used metaphorical thinking to help them to see the complexity and potentiality of a situation, and to go beyond the existing understanding.

Professors and physicians too often present themselves as having "definitive knowledge" about a subject. For people who already have "definitive knowledge" about something, anomalous facts (if they are perceived at all) will simply remain anomalous and will be quickly forgotten. The things they produce will be extensions of what already exists. For others, things that aren't easily explained have special interest, and cause them to ask new questions. New perspectives can lead to new possibilities and new realities.

Once during a lecture, Alfred Korzybski offered his students some cookies, which they seemed to enjoy, then he showed them a label on the bag, "dog cookies," and some of them felt sick. "I have just demonstrated that people don't just eat food, but also words, and that the taste of the former is often outdone by the taste of the latter." Hypnotists have often demonstrated that words can have physiological effects.

Many of our institutions use language as a system for preserving culture, that is, for preventing change. Korzybski wanted to correct the cultural habit of making abstractions seem like objects or "elements," by making people aware of the degree of abstraction in their words. This can be useful, but his book has been used to promote an extreme

linguistic relativism in the theory of knowledge and science, placing "meaning" entirely within the nervous system.

This approach evades the fact that patterns exist objectively, and that they can be perceived as they unfold through time. Although Korzybski thought he was teaching people to overcome the limitations of thinking in the style of Aristotle or Plato, he was supporting an attitude that would make it impossible to perceive in the style of Heraclitus.

If Heraclitus said it's impossible to step in the same river twice, his comment was directed to those who ignore the rich complexity of experience because of stereotyped "elemental" thinking. He was pointing to the abundance of the world, but elemental-concept thinkers have felt that he simply negated their objective meanings.

To perceive another person accurately requires the ability to perceive the person as a pattern unfolding coherently through time, as a potential realizing itself. Carl Rogers' insight was that one's awareness of being perceived in this way encourages the unfolding of potentials.

The refusal of institutions or individuals to perceive others in this way is an imposition of their way of understanding, and is itself a form of oppression. People who think in terms of "professional training" often describe learning in terms of "conditioned reflexes," producing a desired response to each stimulus.

The terms "conditioned reflex" and "conditioning" were introduced into psychology by the behaviorist J. B. Watson, who mistranslated and misrepresented Pavlov's ideas, and who insisted that the ideas of consciousness, volition, and self should be eliminated from the science of psychology.

The orienting reflex, the alertness provoked by something new, was described by Sechenov in 1863, and explored by Pavlov (who also called it the "what is that? reflex" and the "exploration reflex") who considered it to be our most basic and most powerful reflex. The fact that novelty powerfully arouses our exploratory systems means that we have a mental image of our familiar environment, and that a change in that environment requires us to investigate the properties of the new thing, to see whether it can be explained by the things we already know, or whether it requires us to change our basic ideas about our place in our surroundings. For Pavlov, the study of psychology or physiology without consciousness was simply crazy.

Pavlov said that he studied nutrition to understand consciousness and the nervous system, because eating is our closest interaction with the world. Our brain is part of our digestive system. But eating has become highly institutionalized and influenced by our cultural beliefs. If people begin to think about the meanings of eating, they are beginning a process of cultural and philosophical criticism.

Helping people with physical problems (such as obesity, headaches or joint or nerve pain, or named diseases) and helping people who want to understand something about the world beyond themselves, are structurally similar, but in the issues of health the questions and the potential answers are more clearly present and immediate.

The Synectics group began with the study of artistic creation, but they found that it was easier to evaluate their progress when they concentrated on technical invention. They found, as Pavlov had, that consciousness and meaning could best be studied in concrete situations. The process of goal-seeking was to be studied in action.

I see the therapeutic or educational or productive situation as a goal-directed biological and social interaction, and the goal can be either the creation of something new and better, or simply the preservation and application of something already existing.

Until just about a generation ago, "teleology" (especially in biological explanation) was considered to be metaphysical and inappropriate for science. Norbert Wiener, who coined the word "cybernetics" (from Greek for "proficient pilot" or "good steersman") helped to change attitudes toward the word when he used the phrase "teleological mechanism" to describe cybernetic control systems.

A goal-directed system is one that senses its actions and makes adaptations so that its actions can be refined to achieve a purpose. Between 1932 and 1935, a student and colleague of Pavlov's, P. K. Anokhin, developed this idea of self-regulating systems, and originated the concept of feedback, in describing the ways organisms guide themselves and their adaptations. Building on Pavlov's work, and investigating the origins of innate reflexes, he found principles that would explain the origin of organs and their functions, and that would also apply to the interactions between individuals. The functional system on any level, in embryology, psychology, or society, is a sequence of interactions with a useful result. Movement towards a goal is adaptive, and the system is shaped by the

adaptations it makes in moving toward the goal. Resources are mobilized to meet needs, changing the system as it moves towards its goal.

Since there is always novelty in the real world as contexts change, the exploratory function is causing us to continually revise our understanding. Every question forms a functional system, and our brain adapts as we find answers.

This kind of systems theory and self-regulation theory developed along with the field theories in embryology, psychology, chemistry, and some branches of physics. Pattern and analogy were central to their approach. The functional systems are processes that occupy time and space.

The "field" idea in biology (wholes shaping themselves) can be understood by considering its opposite, the belief that cells are guided by their genes (producing a mosaic of parts). That idea, in its extreme form, claimed that cells contained an internal map and an internal clock telling them when and where to move and how to change their form and function as they matured and aged. In reality, cells communicate with surrounding cells and with the material between cells. The existence of long-range ordering processes between atoms, molecules, and cells threatened some of the central dogmas of the sciences.

Although Norbert Wiener popularized some aspects of the "teleological" approach to regulatory systems in the 1950s, and saw analogies between the teleological machines and the way the brain functions in Parkinson's disease, by 1950 the digital approach to information processing, storage, and transmission was displacing analog devices in computation and engineering, and was compatible with theories of intelligence, such as neo-Kantianism, that believed that human intelligence can be defined precisely, in terms of discrete rules and operations. Field thinking in embryology, cancer theory, psychology, and other sciences effectively disappeared—or "was disappeared," for ideological reasons.

Wiener's goal-directed machines, like Anokhin's functional systems, worked in space and time, and the idea of steering or guidance assumes a context of time and space in which the adjustments or adaptations are made. Analog computers and control systems in various ways involved formal parallels with reality. The components of the system, like reality, occupied space and time.

Digital computers, with their different history and functions, for example their use for creating or breaking military codes, didn't intrin-

sically model reality in any way. Information had to be encoded and processed by systems of definitions. A sequence of binary digits has meaning only in terms of someone's arbitrary definitions.

Parallel with the development of electronic digital computing machines, binary digital theories of brain function were being developed, by people who subscribed to views of knowledge very different from those of Anokhin and Wiener. (Anokhin argued against the idea that nerves use a simple binary code.) These computer models of intelligence justify educational practices based on authoritative knowledge and conditioned (arbitrary) reflexes. Neo-Kantianism has been the dominant academic philosophy in the U.S., turning philosophy into epistemology to exclude ontology. "Operationism" and logical positivism share with neo-Kantianism its elimination of ontology (concern with being itself).

In the 1960s, Ludwig von Bertalanffy developed a theory of systems, defining a system as an "arrayed multitude of inter-linked elements." Although it was intended as a description of biological systems, it reduced the teleological factors, needs and goals, to a kind of mechanical inner program, such as "regulatory genes." "Following old modes of thought, some called this orderliness of life 'purposiveness' and sought for the 'purpose' of an organ or function. However, in the concept of a 'purpose' a desiring or intending of the goal always appeared to be involved—the type of idea to which the natural scientist is justly unsympathetic" (von Bertalanffy).

His system theory was highly compatible with programmed digital computers, that could define the interactions of "elements," but unlike Anokhin's definition of functional systems, it lacked a pattern-forming mechanism. In Anokhin's view, the system is formed by seeking its goal, and perceiving its progress toward the goal.

Carl Rogers' approach to person-centered processes recognized that the interacting therapist and client or teacher and student were a formative system, rather than just an occasion for one to inform the other.

In the Synectics group, they learned to identify the types of deeply involved interaction that would lead to the best inventions. As in Anokhin's functional systems, resources are mobilized or generated as they are needed. Like Anokhin, they showed that the process of creating something new can be understood and controlled.

Every meaningful interaction involves formative systems.

Stimulation of sensory nerves can cause cells to move into the stimulated area, causing the organ to grow. Environmental enrichment causes brains to become larger, and to metabolize at a higher rate. All of these processes, from the level of energy production to the birth of new cells and the creation of new patterns in the brain, are called up in the formation of a functional system.

The studies of organismic coherence by Mae-Wan Ho and Fritz Popp appear to support the idea that even the alignment of molecules in cells is responsive to the state of the entire organism.

The reason this seems implausible to most biologists is that cells are commonly still seen as analogous to little test-tubes in which chemical processes occur as the result of random collisions between molecules floating in water. But Sidney Bernhard's study of glycolysis showed that the reactive sugar molecules are passed individually from one enzyme to the next, in an orderly manner.

In this system, the flow of energy, a series of oxidations and reductions changing glucose into other substances, effectively "pulls" the molecules through the system, contributing to order on a molecular level. Function creates structure, which supports function.

Self-regulating systems are self-ordering systems. When a person is allowed to function freely as a goal-directed, questioning system, the formation of patterns in the brain will be spontaneous and appropriate, and orderly. Knowing is the ability to hold patterns in awareness. Knowledge, rather than being stored like money in the bank, is something that is regenerated, or generated, as we need it.

When our own steering system is commandeered by the authorities, our patterns of knowledge will be compartmented, and arranged in a fixed pattern. This kind of knowledge either deteriorates, or it seeks more of its own kind.

While self-regulation and the generation of knowledge are pleasurable, having knowledge imposed isn't.

Korzybski was right in warning about the dangers of letting names become "elements." This perception led Paolo Freire to emphasize the educational importance of critically giving things their appropriate names, rather than just "banking" the names given by an authority. "To exist, humanly, is to name the world, to change it. Once named, the world in its turn reappears to the namers as a problem and requires of them a new naming. Human beings are not built in silence, but in word,

in work, in action-reflection." "…to speak a true word is to transform the world." "'Problem-posing' education, responding to the essence of consciousness—intentionality-rejects communiques and embodies communication".[1]

Having the power to assign names is a source of power and wealth. The pharmaceutical industry has been accused of inventing new diseases to sell new drugs for treating them. Old definitions of cancer are hard to change, when the medical profession has invested so much in treatments—radiation and cytotoxic chemotherapy—which conflict with newer biological understanding of cancer.

The person who is learning is critically interacting with both nature and culture, with practical issues and theories.

Applying this to practical problems of health and nutrition, a first step is to begin to think about which things are theories or deductions from theories, which are habits, and which things are felt needs or appetites, and to get in the habit of watching processes or things—such as "signs" and "symptoms"—develop through time.

With practice, people can begin to see themselves as functional systems in their main activities, such as eating, and to watch how their needs influence their actions, and what effects different ways of eating have on their other functions, such as sleeping and working. Do appetites govern the timing of meals and the choice of foods? How does the time of day or time of month affect appetites? People often watch for effects of foods, but usually only for a few minutes or hours after eating. Some foods can produce symptoms days after they were eaten, and the activation of the digestive system by a recent meal can cause a reaction to something eaten previously.

Our traditional cultures, and advertising and schools give us definitions and expectations relating to foods and symptoms and physiology, and they teach us to think of our bodies in terms of an "immune system," "endocrine system," "digestive system," "nervous system," and "circulatory system," which are mainly anatomical concepts that are more useful to the drug companies than to the consumer of culture. Both conventional and alternative approaches to medicine and health are likely to let those arbitrary ideas of systems cause them to overlook real, but unnamed, processes.

When the organism is seen as a mosaic of parts, rather than as a system of developing fields, medical treatments for one part, such as

the "circulatory system," are likely to cause problems in other "systems," because the "parts" being treated don't exist as such in the real organism, with the result that the treatments are seldom biologically reasonable.

Besides learning to perceive one's own physiology and becoming aware of the processes of perceiving and knowing so that they can be improved, it's important to seek information to expand the interpretive framework, and to look for new contexts and implications.

Reading with a critical imagination is as important for science as it is for literature or advertising. Good literature often opens expansive new ways of seeing the world, and good science writing can do that too, but too often scientific publications have ulterior motives, and should be read the way advertising propaganda is read.

Some publications now require authors to state their conflicts of interest (such as receiving money from a drug company while testing a drug), but editors and publishers, who choose which studies will be published, seldom reveal their conflicts of interest. As Marcia Angell showed, editorial choices can turn statistical randomness into statistical significance. Private ownership of science journals permits control of their content.

Besides being aware of the conflicts of interest and the frequent insignificance of "statistical significance," it's possible to recognize some features of the style of argument which is often used in science propaganda. A deductive style, rather than a descriptive and inductive style is extremely common in technical writing, and it should always lead the reader to question the principle from which deductions are made.

"Membranes are made from Essential Fatty Acids, therefore those fatty acids are nutritionally essential." But cells can multiply in a culture medium that provides no fats. In biology, the most popular "principles" are simply dogmatic beliefs about genes and membranes.

In physics, where testable inferences can be drawn from arbitrary assumptions or doctrines, predictions that may be made based on different assumptions are often ignored for ideological reasons. This ideological quality of physics can permeate the other sciences when they use reductionist explanations.

Korzybski felt he was helping humanity to escape "word magic" and to advance to a mathematical view of the world. But the same processes that caused people to "confuse words with things" can cause people to confuse mathematical descriptions with reality.

"Chaos theory," which was a faddish excitement about the ability to generate unpredictable output from a simple rule (which could be endlessly repeated by a computer), has been suggested to explain many things in biology, including heart rate variability. It doesn't. Instead, it has probably had a slightly harmful effect, by distracting attention from real biological pattern- forming processes.

Real substance can sometimes be modeled by descriptions of randomness, but substances at all levels have intrinsic pattern-forming tendencies, and context-dependent histories. Water, for example, has structure and structural memory that can affect even simple chemical reactions, and even gases have internal complexities that are often ignored. Real observations shouldn't be displaced by theories. The ideal and identical atoms of the reductionists are a crude fantasy, invented, more or less consciously, to serve their ideological purposes. One purpose has been to justify their abstract models of reality. A particularly noxious way of modeling reality has been based on the assumption of randomness, justifying a statistical view of all things.

The neo-Kantian philosophy that has dominated U.S. universities for more than a century argues that our senses (even when extended instrumentally) are limited, so our knowledge must be limited—we can only speak of theories or interpretations, not of being. The world we see is, according to them, only an artifact of our senses. A popular example is that the flower a bee sees is different from the flower a human sees, because the bee's eye is sensitive to ultraviolet light. (The triviality of the example is shown by the fact that when a person's lens is removed because of a cataract, ultraviolet light becomes visible, because it is no longer blocked by the tissue that is many times thicker than a bee's lens.) There is a straw-man quality to their arguments against philosophical realism and empirical science: No one claims that our senses deliver complete knowledge all at once. What the realists claim is that interacting with the world is an endless source of valid knowledge.

When reading science articles, or listening to lectures, and even while privately thinking about experiences, it can be useful to watch for the improper use of assumptions. Our understanding has been shaped by the assumptions of our culture, and these assumptions present an attitude toward the nature of the world, in some cases even about the ontology that our philosophers have said is beyond our reach. "Evolution is shaped by random mutations," "nuclear decay is random," "the universe

is expanding," "entropy only increases," "DNA controls inheritance," "membrane pumps keep cells alive," and all of the negative assumptions that have for so long denied the systematic generation of order.

Every communicative interaction is an opportunity for the discovery of new meanings and potentials.

Aristotelian motto: If the knower and the known form a functional system they are substantially the same.

Immunodeficiency, Dioxins, Stress, and the Hormones

Ray Peat's Newsletter, 2006

It has been over ten years since I wrote about "AIDS"[1] and the official doctrine that it is caused by the "HIV" virus still hasn't been supported by anything that resembles real science. Duesberg's arguments have never been answered (except by bureaucratic thuggery).

In 1989 I pointed out that septicemia, blood stream infection, in young adults, which used to be a rare thing, and which indicates defective immunity, has been increasing in a remarkably continuous way since

Critical Points

- There are many toxins which modify hormonal responses, activating cells and altering the immune system (including estrogens and dioxins.) When these act early in life, extremely small amounts can cause life-long changes.
- When respiratory energy production is blocked in stimulated cells, the cells are likely to die. (Cortisol, estrogen, polyunsaturated oils have this effect, especially on thymus cells.)
- Antibodies are involved in removing the debris of cells that have disintegrated. Intense cellular damage causes many "autoantibodies" to be produced. People with AIDS have a high incidence of "autoimmunity."
- Endogenous retroviruses are activated by toxins known to be associated with immunodeficiency. Everyone has endogenous retroviruses. The antibodies which are used to diagnose "HIV" infection can, in the demonstrated absence of that virus, be produced in connection with lupus, Sjogren's syndrome, and arthritis. These autoimmune conditions are promoted by estrogen.
- Estrogen activates the production of cortisol, and damages the normal feedback control, causing both cortisol and ACTH to be elevated.
- Estrogen causes chronically elevated free fatty acids, and synergizes with unsaturated fats.
- Estrogen inhibits thyroid function.
- Hypercortisolism is typically associated with hypothyroidism, and both tend to cause the loss of lean body mass.
- AIDS is often compared to Addison's disease, because of hyponatremia (loss of sodium) and fatigue. Hypothyroidism causes hyponatremia and many other features seen in AIDS.
- Increased levels of cortisol, estrogen, and polyunsaturated fatty acids, and decreased levels of the active thyroid hormone (T_3) and (placental) progesterone have been found to occur in AIDS.
- Progesterone can contribute to the inhibition of HIV replication and transmission.
- Common environmental factors can produce hormonal changes leading to immunodeficiency.

the late 1940s, and I reviewed the many things in our environment that are known to suppress immunity, and which have become increasingly prevalent in our environment-unsaturated vegetable oils, ferrous iron and carrageenan in our foods, lead in air, food, and water, exposure to medical, military, and industrial ionizing radiation, vaccinations, pesticides, chlorinated hydrocarbons, nitric oxide (smog and medications) and oral contraceptives and environmental estrogens, in particular. Of these factors, only radiation and lead exposure have decreased in the last several years, after several decades of rapid increase. The widespread use of diuretics in pregnancy, which began in the 1950s and contributed to an epidemic of premature births, also declined after the late 1960s. Most of these environmental factors damage the thymus gland, which regulates the immune system, and by acting on the thymus their effects tend to be additive with other immunosuppressive factors, including cancer, traumatic injury, inflammation, toxins in spoiled food (e.g., aflatoxins) and malnutrition.

Cancer, AIDS, and extreme hypothyroidism have several features in common—they cause tissue loss and organ damage, with immunodeficiency and intense activation of the stress hormones, including cortisol. In cancer and AIDS, a good case has been made for the primacy of stress-induced wasting as the main cause of death. Whatever one might believe to be the cause of cancer and AIDS, it is always good for the patient to prevent tissue damage from the stress associated with the sickness. Since the stress hormones primarily destroy tissues by the activation of specific proteases, the use of protease inhibitors for treating AIDS could conceivably be affecting the stress response. However, the body's normal protection against the cortisol-activated proteases is centered on the protective hormones, progesterone, thyroid, and the androgens.

One hospital in southern Vietnam admitted 437 septicemia patients between mid-1993 and 1994; 23 % of the adults died.

In 8 months, 17,000 seals died of infections in Europe. In California, many seals die with an unusual form of metastatic cancer. Seals are highly contaminated with industrial dioxins.

In Africa, aflatoxin is strongly associated with immunodeficiency. In animals, both dioxin and aflatoxin activate the expression of viruses.

Endometriosis is stimulated by dioxins. Environmental estrogens affect the immune system.

Environmental Stress

One of the most broadly substantiated principles in biology is that a great variety of harmful causes all lead to a few forms of biological harm—the concept of the stress reaction shows the powerful implications of the principle. Stress, no matter what the specific cause, has a particularly destructive effect on three organ systems: The nervous system, the immune system, and the reproductive system. Inflammation, lipid peroxidation, tissue atrophy, the "calcium catastrophe" (when almost anything goes wrong, calcium can transmit and amplify and extend the problem, but isn't itself the source of the problem), mitochondrial decay, and similar events help to define the stress reaction in greater detail.

Hans Selye showed that the thymus shrinks very early in the stress reaction. In his understanding of the process, when adaptation was followed by the "exhaustion phase," the adrenal glands had simply become exhausted from overuse. F. Z. Meerson's work showed that cortisol, and the free fatty acids mobilized by stress, have a toxic influence on the mitochondrial energy production system. Both cortisol and the free fatty acids block the efficient use of glucose for producing energy, creating a diabetes-like condition. The exhaustion problem caused by excessive stress is generalized, not just a matter of adrenal insufficiency.

Meerson's work created the basis for undersanding several degenerative processes, especially the phenomenon of "excitotoxicity," in which the combination of excessive stimulation and deficient energy supply damages or kills cells.

Selye believed that some hormones are antagonistic to each other. A few of the oppositions that he identified have been thoroughly researched, especially the catabolic/anabolic functions of glucocorticoids and androgens, and the shock/antishock functions of estrogen and progesterone, respectively.

Puberty, because of hormonal changes, especially increased estrogen, can be seen as the first stage of a chronic stress, resembling diabetes, since elevated free fatty acids cause "insulin resistance," with slightly impaired oxidation of glucose. The thymus shrinks considerably at puberty, under the influence of the hormonal changes and the increased free fatty acids (caused mainly by estrogen). The degenerative diseases can be seen as the cumulative result of stress, in which tissue damage results from the diabetes-like impairment of energy production.

The thymus, and the thymus-dependent areas of the spleen, are required for full and subtle control of immunity. In the absence of thymic control, the B cells are still able to produce antibodies, but they are more likely to produce autoantibodies.

Stress produces a variety of cellular changes, including the production of the "shock proteins." These proteins can make up 20 % of the cell's total protein content. In themselves, the shock proteins are immunosuppressive. They can be recognized by the immune system as antigens, and so are a factor in the appearance of "autoimmune" antibodies. The autoantibodies themselves are often blamed for the diseases they are sometimes associated with, but since they can be present (for example, following removal of the spleen) in people who have no symptoms, their function is probably to facilitate the removal of tissues which are defective for some other reason. The shock proteins could be one of the signals that activate the immune system to remove damaged tissue, and they might be involved in the removal of senescent cells, though I don't think any experiments have been done to test this idea.

Besides activating the cells to produce massive amounts of the shock proteins, stress can also activate the so-called hormone receptors, such as estrogen receptors, even in the absence of the hormones. Stress also activates the endonucleases, which cut sections out of the DNA molecules, and activates mobile genetic elements, producing genetic instability. Like cortisol and estrogen, stress itself activates integrated retroviruses. The "endogenous retroviruses" make up nearly 10 % of the human genome, and many of them locate themselves in regulatory sites in the chromosomes.

Since stress lowers the discriminatory ability of the immune system, and stimulates the expression of retroviruses, the antibodies sometimes seen in association with immunodeficiency may be similar to the various autoantibodies that are also produced by stress.

People who have autoimmune diseases such as lupus and Sjogrens syndrome (which are promoted by estrogen: Ahmed and Talal) have antibodies which sometimes react positively in the AIDS test, and searches for the HIV virus in such people have found no evidence of it.[2,3] Treatments for roundworms and other parasites cause antibodies to retroviruses to appear in animals that previously tested negative; this might account for the high rates of positive tests for HIV in areas such as Africa in which treatment for filiariasis is common.[4]

Organisms are most sensitive to environmental damage early in life, especially prenatally. This is the period in which normal hormone exposure masculinizes the brain, for example. The term "imprinting" refers to the extreme responsiveness of the organism at this time, and it has been extended to include long lasting influences which may result from abnormally high or low levels of natural substances, or from the presence of other, abnormal substances during the sensitive period. The effects of early "imprinting" can cause permanently altered sensitivities. In animal studies, L. C. Strong showed that prenatal influences determine the age at which puberty and reproductive senescence occur. In humans, premature birth, a powerful stressor, is associated with premature puberty. The thymus is damaged both by premature birth and by puberty. The effects of damage early in life will increase vulnerability in subsequent decades.

When babies are imprinted by the mother's disturbed hormones, or by diuretics, by milk substitutes, or by industrial effluents, the worst effects are likely to be seen decades later, or even generations later. A similar long-range effect can be produced by nutritional deficiencies.

Although more mature organisms are less sensitive to stress, both early imprinting, and the cumulative effects of exposure, will cause some individuals to be much more sensitive than others, and aging itself increases vulnerability.

If the present epidemic of immunodeficiency is produced by environmental stress, then we should expect to see a variety of other stress-related diseases increasing at roughly the same time. When a stressor is acting through imprinting, then the harmful effects may not be seen until 20 or 30 years later, but when the stressor has acute and immediate effects, the effects should rise and fall at roughly the same time as the environmental cause.

The rise of the Acquired Immunodeficiency Syndrome during the last 50 years hasn't been the only health problem that has grown rapidly during that time. The "flesh eating bacteria," causing necrotizing fasciitis and related conditions, should probably be classed along with septicemia/bacteremia as the consequence of a weakened immune system, but there are many other diseases that have followed a similar pattern, which might be caused by the same factors which are causing immunodeficiency. Thyroid diseases (mostly in women), some autoimmune diseases including primary biliary cirrhosis (mostly in women) and

inflammatory bowel disease, liver cancer, diabetes (doubling in children since 1949), prostate cancer, decreased sperm counts, premature births and birth defects, minimal brain dysfunction-attention deficit-hyperactivity, cerebral palsy, premature puberty (which is associated with premature birth), congestive heart failure, osteoporosis (independently of the changing age-structure of the population), depression (most common in women, more than doubling among children in recent decades), and multiple sclerosis have increased in prevalence during this period. Some of these conditions are strongly associated with each other, for example, primary biliary cirrhosis, breast cancer, and osteoporosis. It is common knowledge, among people who study immunity, that radiation, polyunsaturated fatty acids, estrogens, and dioxins are toxic to the thymus gland, and can produce immuno-deficiency. They mimic or accelerate the thymic atrophy of aging, causing a deficient thymus-dependent immune response, usually without harming the ability of B cells to produce antibodies. There are probably many examples of damage to immune systems, besides immunodeficiency, caused by these agents. Slight damage to the immune system, such as can be produced by hypoglycemia or other energy deficit—creates an exaggerated inflammatory response, and the release of the mediators of inflammation, including histamine, serotonin, and prostaglandins, activates the stress hormone system, leading to further biological damage. Liver disease and several other "autoimmune" diseases involve abnormal immune responses, probably including thymic deficiency and an intensified inflammatory response. The fact that livers transplanted from female donors to male recipients are less successful than are livers from male donor transplanted into female recipients, is consistent with the idea that autoantibodies (which are far more common in women than in men) are a relatively harmless response to changes in the organs themselves.

Are antiviral therapies working? Ivan Ilich, in *Medical Nemesis*, showed that historically, many diseases have had characteristic incidence curves, rising to a maximum, and then falling away to relative insignificance, independently of what people were doing as treatment or prevention. As susceptible people are exposed to conditions that cause a disease, they will get sick, and then either die or develop resistance. The conditions which at first caused increasing disease incidence, will eventually tend to affect only children who haven't developed resistance.

If AIDS mortality rose rapidly to a peak a few years ago, and then began falling, we should ask whether this pattern fits that of other diseases discussed by Ilich. Looking for causes other than the virus, we might find a parallel in the rise and fall of some other factor.

In the 1950s, new diuretics came on the market, and millions of pregnant women took them. It was predicted that there would be an epidemic of brain damage as a result, and in fact the incidence of hyperactivity, attention-deficit, and other "minimal" brain damage disorders did rise during those years. After about 15–20 years, experiences such as the Thalidomide episode caused physicians to temper their enthusiasm for the use of drugs during pregnancy. The incidence of low birthweight babies in the U.S. peaked around 1965, and 28 years later AIDS mortality in the U.S. peaked. The rising curve had followed both the increase in radioactive fallout from atmospheric testing of large numbers of atomic bombs up to 1963, and the intense promotion of the new diuretics beginning in the early 1950s. The peak in AIDS mortality in 1993 came ten or twelve years after the long decline in SAT scores had stopped. (The most extreme declines in SAT scores had occurred among the brightest students, disproving the contention that the average score fell simply because more students were taking the tests.) The same prenatal damage which caused the extreme decline in SAT scores 18 years later (when the damaged babies reached that age) would have left many of the same individuals with weakened immune systems, which would fail prematurely, but at varying intervals, depending on the exposure to other factors.

The use of unleaded gasoline increased into the 1990s, and there was a corresponding decrease in tissue lead content, reflecting the smaller amount of lead being put into the environment. According to some reports, medical and dental x-ray exposures were declining during this period. Yet other factors, including dioxins and unsaturated dietary fats, were probably increasing.

Although the new protease inhibitors wouldn't be used until years after the AIDS mortality had begun falling, the government and drug companies are claiming that it is the drugs which are decreasing the mortality.

A Synthesis

Many things in our environment are increasing the incidence of certain kinds of liver disease. The liver processes things that are ingested or that enter the blood stream after being inhaled or absorbed through the skin, so in a toxic environment it is susceptible to injury. If deprived of good nutrition or adequate thyroid hormone it is especially sensitive to toxins. The body's own estrogen is a burden on the liver, causing women's livers to be on average slower than men's in processing environmental chemicals.

Almost any kind of toxin causes the liver to be less efficient at excreting other substances, including hormones. In malnutrition, sickness, and in aging, there is a tendency for higher levels of estrogen to remain circulating in the blood.

Natural estrogen, and environmental substances that act like estrogen, act as excitants in many types of cell, and at the same time, reduce the efficiency of energy production. Both of these properties relate to its known ability to activate the adrenal glands. A. L. Soderwall, who was my thesis adviser at the University of Oregon, found that estrogen caused hamsters' adrenal glands to enlarge, and that larger doses overstimulated the glands sufficiently to cause tissue damage. It is now known that estrogen acts directly on the adrenal cells to stimulate cortisol production, and that it also stimulates the pituitary to produce more adrenocorticotropin (ACTH), which also stimulates the adrenals; estrogen's effect is to impair the negative feedback, in which cortisol normally shuts down ACTH production. This impaired feedback is characteristic of aging.

Estrogen directly causes the thymus gland to atrophy, and several of its effects, such as increased adrenal activity and elevated free fatty acids, also contribute to the shrinkage of the thymus and the inhibition of its functions. While this is happening, the B cells, which normally are under the control of the thymus cells, are not killed by estrogen, and actually seem to be stimulated by estrogen to produce certain types of antibodies. This combination of effects, weakening the thymus and stimulating antibody production, is thought to contribute to the development of autoimmune diseases. Estrogen also stimulates mast cells and similar cells to release histamine and other promoters of inflammation, and these effects are probably closer to the actual problem in the autoim-

mune diseases. Several of the substances formed under the influence of estrogen interfere with energy production and contribute to cellular excitation, causing tissue injury.

Cortisol also stimulates antibody production while suppressing thymic immunity.[5]

Estrogen and stress cause increased levels of free fatty acids to circulate. The polyunsaturated fatty acids are immunosuppressive, antithyroid, diabetogenic, inhibit respiration, and promote the actions of estrogen and cortisol.

People suffering from AIDS have been found to have increased estrogen, with high cortisol and ACTH, and very low T_3. (Unfortunately, some researchers and the editors who publish their ideas, conclude that the hormones don't cause the stress and wasting symptoms, because they call thyroid a "catabolic hormone," and because they describe the fatigue and sodium deficiency as evidence of "deficiency of cortisol." Such is the state of the research establishment.)

In animal experiments, and a few human tests, the HIV and similar viruses have produced effects that could plausibly explain some of the conditions seen in AIDS, such as damage to brain cells (C. Pert, R. Sapolsky), and altered steroid secretion. But this is real science, that promises to link up with information about stress, aging, allergy, and biological adaptability.

For example, Sapolsky's group[6] found that the nerve toxicity caused by a viral protein (called gp120) synergizes with glucocorticoid toxicity, lowering the ATP level and inhibiting mitochondrial function, and that simply supplying the nerve with additional energy protects it from destruction. In other words, the viral peptide just increases excitotoxicity.

Another group[7] found that the presence of the virus can decrease the production of progesterone. Since progesterone blocks[8] the expression (and transmission) of the virus, this suggests how the overgrowth of the virus might be triggered by stress—once progesterone synthesis falls, a vicious circle could get started.

Lee, et al., found that progesterone can help to prevent transmission of the virus from an infected mother to the fetus. But the most interesting study of the virus in pregnancy involved mice that were engineered to contain extremely large quantities of the HIV provirus.[9] At birth, they seemed normal, but within a few days their skin became diseased, and they quickly wasted away and died. The experimenters realized

that something present in the mother's body had permitted normal development up to the point of birth, and then the wasting disease set in. The placental hormone, chorionic gonadotropin, is produced in large amounts during pregnancy. The experimenters gave newborn infected mice regular doses of human chorionic gonadotropin (hCG), and they developed normally.

Rodents don't respond to gonadotropins or other ovarian stimulation exactly the way pigs and primates and people do. For example, prolactin and melatonin usually inhibit progesterone synthesis in people, but in rodents, they increase it. So it's necessary to see exactly what happens to the ovarian hormones when a mouse is given hCG. In 1996, another group (H. Krzanowska and M. Szoltys) had done that, and found that hCG greatly increases progesterone synthesis, but decreases estrogen.

Considering the progesterone-HIV experiments together, I am reminded of a science fiction movie, in which a disease from another planet killed everyone in the lab that was studying it, except for one woman, who turned out to be pregnant.

The medical version of AIDS research, though, pushes aside all of the real science, in favor of a simplistic idea that the virus kills the cells of the immune system, and uses false diagnostic methods and deadly drugs to treat something which too often doesn't exist, while denying that there are other real causes of immune deficiency and wasting-sickness, etc.

Aging is characterized by loss of lean body mass, immunodeficiency, and a variety of autoimmune reactions. My perennial argument has been that decreased thyroid and progesterone, associated with increased estrogen and stress hormones, are largely responsible for those changes. The huge investment in AIDS research has found that these occur in AIDS, but, because of the medical pharmaceutical culture which has created myths about these hormones, no one is yet interpreting the hormone imbalances in ways that would reveal their responsibility for the symptoms. While the institutionalized theory claims that the HIV virus is responsible for the syndrome, the hormones are reduced to epiphenomena.

Intelligence and Metabolism

Ray Peat's Newsletter, 2009

- Appropriate stimulation is an essential part of the developmental process. Inappropriate stimulation is a stress that deforms the process of growth. Mediators of stress, such as serotonin, can cause persistent distortions of physiology and behavior.
- Education can either activate or suppress mental energy. If it is mainly obedience training, it suppresses energy. If it creates social dislocations, it disturbs mental and emotional energy.
- Stress early in life can impair learning, cause aggressive or compulsive behavior, learned helplessness, shyness, alcoholism, and other problems.
- Serotonin activates the glucocorticoid system, which can produce brain atrophy. Antiserotonin agents protect against brain atrophy and many other effects of stress. The brain-protecting neurosteroids, including pregnenolone and progesterone, which are increased by some kinds of stimulation, are decreased by isolation stress, and in their absence, serotonin and the glucocorticoids are relatively unopposed.
- Since excess serotonin can cause thrombosis and vasospasms, and the excess cortisol resulting from hyperserotonemia can weaken blood vessels and the immune system, a person's longevity is likely to be shortened if something doesn't intervene to alter the patterns induced by stress early in life.

Baroness Blatch: "My Lords, the levels of achievement are well above the national average of our own state schools."

"This is a school which attained 75 per cent A to C passes in 1998, and 63.9 per cent in 1999. Those figures are well above national averages. There is no truancy; and there is the highest possible level of parental satisfaction with the school. When those parents are paying their money and know what they are paying for, who are we to take a different view about the philosophy of education in a private school?"

Comment during debate in House of Lords, June 30, 1999, on Chief Inspector of Schools Woodhead's threat to close Summerhill, a democratic school which had been started in 1921.

In 1927, the government inspectors had recommended that "all educationalists" should come to Summerhill to see its "invaluable" research, which demonstrated that

HAVING written about animal intelligence, and the ways in which it is similar to human intelligence, now I want those ideas to serve as a context for thinking about human intelligence without many of the usual preconceptions.

Intelligence is an interface between physiology and the environment, so it's necessary to think about each aspect in relation to the other. Things, both biochemical and social, that enhance intelligence enhance life itself, and vice versa.

Psychologists have tried to give their own definitions to words like idiot, imbecile, moron, and genius, but they have just been refining the clichés of the culture, in which "dummy" is one of the first words that kids in the U.S. learn. Many psychologists have tried to create "culture-free" tests of intelligence, making it clear that they believe in something like innate animal intelligence, though they usually call it "genetic" intelligence. Other psychometrists have transcended not only biology but even rationality, and have catalogued the preferences of people that they define as intelligent, and designed "I.Q. tests" based on the selection of things that were preferred by "intelligent people." This behavior is remarkably similar to the "psychometry" of the general culture, in which "smart" people are those who do things the "right" way.

About thirty years ago, someone found that the speed with which the iris contracts in response to a flash of light corresponds very closely to the I.Q. measured by a psychologist using a standard intelligence test. The devices used to measure reaction time in drivers' education courses also give a good indication of a person's intelligence, but so does measuring their heart rate, or taking their temperature. Colleges would probably be embarrassed to admit students on the basis of their temperature (though they commonly award scholarships on the basis of the ability to throw a ball). Colleges, to the extent that they are serious about the business of education, are interested in the student's ability to master the culture.

The way a person has learned during childhood can shape that person's manner of grasping the culture. To simply accelerate the learning of a standard curriculum will increase that person's "I.Q." on a conventional test, but the important issue is whether it is really intelligent to learn and to value the things taught in those curricula. Some educators say

students' development is better when they regulate themselves and are not required to attend lessons.

that their purpose is to socialize and indoctrinate the students into their discipline, others believe their purpose is to help their students to develop their minds. Both of these approaches may operate within the idea that "the culture" is something like a museum, and that students should become curators of the collection, or of some part of it. If we see the culture metaphorically as a mixture of madhouse, prison, factory, and theater, the idea of "developing the student's mind" will suggest very different methods and different attitudes toward "the curriculum"

Even sophisticated people can fall into stereotyped thinking when they write about issues of intelligence. For example, no one considers it a sign of genius when a slum kid is fluent in both Spanish and English, but when some of history's brightest people are discussed, the fact that they learned classical Greek at an early age is always mentioned. No one mentions whether they were competent in idiomatic Spanish.

One of the old cultural stereotypes is that child prodigies always "burn out," as if they were consuming a fixed amount of mental energy at an accelerated rate. (This idea of burn-out is isomorphic with the other cultural stereotypes relating aging to the "rate of living," for example that people with slow heart beats will live longer.) Some of the men who have been considered as the world's brightest have, in fact, gone through a crisis of depression, and Terman's long-term study of bright people found that "maladjustment" did increase with I.Q., especially among women. But the facts don't support the concept of "burn-out" at all. I think the facts reveal instead a deep flaw in our ideas of education and professional knowledge.

In a world run by corporation executives, university presidents ("football is central to the university's mission"), congressmen, bankers, oilmen, and agency bureaucrats, people with the intelligence of an ant (a warm ant) might seem outlandishly intelligent. This is because the benighted self-interest of the self-appointed ruling class recognizes that objective reality is always a threat to their interests. If people, for example, realized that estrogen therapy and serotonin-active drugs and x-rays and nuclear power and atomic bomb tests were beneficial only to those whose wealth and power derive from them, the whole system would lose stability. Feigned stupidity becomes real stupidity.

But apart from ideologically institutionalized stupidity, there are real variations in the ability to learn, to remember and to apply knowledge, and to solve problems. These variations are generally metabolic

differences, and so will change according to circumstances that affect metabolism. Everyday social experiences affect metabolism, stimulating and supporting some kinds of brain activity, suppressing and punishing others. All of the activities in the child's environment are educational, in one way or another.

Some of the famous prodigies of history illustrate the importance of ideology in the development of intellect. Family ideology, passing on the philosophical orientations of parents and their friends, shapes the way the children are educated.

Some of these family traditions can be traced by considering who the child's godfather was. Jeremy Bentham was John Stuart Mill's godfather, Mill was Bertrand Russell's; Ralph Waldo Emerson was William James' godfather, James was W. J. Sidis's. Willy Sidis was educated by his parents to demonstrate their theory of education, which grew out of the philosophies of Emerson and James. His father, Boris Sidis, was a pioneer in the study of hypnosis, and he believed that suggestion could mobilize the mind's "reserve energy." Willy learned several languages and advanced mathematics at an early age. After he graduated from Harvard at the age of 16, he tried teaching math at Rice Institute, but he was displeased by the attitudes of his students and of the newspaper and magazine writers who made a profession of mocking him. He attended law school at Harvard, and would have been imprisoned as a conscientious objector if the war hadn't ended.

Antisemitism probably played a role in his sense of isolation when he was at Harvard and Rice. In 1912 Henry Goddard, a pioneer in intelligence testing (and author of *The Kallikak Family: A Study in the Heredity of Feeble-Mindedness*), administered intelligence tests to immigrants and determined that 83 % of Jews and 87 % of Russians were "feeble-minded." By the standards of the time, it was highly inappropriate for the child of extremely poor Jewish immigrants from eastern Europe to be so bright.

Sidis hid from the press, and worked as a bookkeeper and clerk, while he studied and wrote. During his years of obscurity, he wrote books on philosophy and American history. Eventually, the journalists discovered him again, and after prolonged lawsuits against the magazines for invasion of privacy and slander, he died of a stroke at the age of 46.

Sidis is probably the culture's favorite example of the child prodigy who burns out, but people (Robert Persig, Buckminster Fuller) who

have read his books have said favorable things about them. The journalists' emphasis on the fact that Sidis never held a prestigious job nicely illustrates their cliché mentality: "If you're so smart, why aren't you rich?" But throughout history, intelligent nonconformists have supported themselves as craft-workers or technicians—Socrates as a stone mason, Spinoza as a lens grinder, Blake as an engraver, Einstein as a patent examiner, for example.

In conventional schools (as in conventional society) 10,000 questions go unanswered, not only because a teacher with many students has no time to answer them, but also because most teachers wouldn't know most of the answers.

The parents of W. J. Sidis and J. S. Mill were remarkably well educated people who, because they dissented from society's ideology, chose to spend much of their time educating their children. Whenever a question about Euclidean geometry or Greek grammar occurred to the child, it could be answered immediately. It was only natural that progress would be fast, but there were more important differences.

When questions are answered, curiosity is rewarded, and the person is enlivened. In school, when following instructions and conforming to a routine is the main business, many questions must go unanswered, and curiosity is punished by the dulling emptiness of the routine.

Some schools are worse than others. For example, slum children were given I.Q. tests when they started school, and each subsequent year, and their I.Q.s dropped with each year of school. In a stimulating environment, the reverse can happen, the I.Q. can rise each year. Since the tests aren't "culture free," their scores reflected the material that they were being taught, but they undoubtedly also reflected the increasing boredom and despair of the children in a bad school, or the increasing liveliness of the children in the stimulating environment.

I have spoken with people in recent years who still held the idea of a fixed genetic mental potential, who believe that poor children fall behind because they are reaching their "genetic limit." For them, the I.Q. represents an index of intrinsic quality, and is as important as distinguishing between caviar and frogs' eggs. The rat research of Marion Diamond and others at the University of California, however, showed that the structure, weight, and biochemistry of a rat's brain changes, according to the amount of environmental stimulation and opportunity for exploration. This improvement of brain structure and function is

passed on to the next generation, giving it a head-start. It isn't likely that rats are more disposed than humans to benefit from mental activity, and in the years since Diamond's research there have been many discoveries showing that brains of all sorts complexify structurally and functionally in response to stimulation.

Rats isolated in little boxes, generation after generation—the normal laboratory rats—were the standard, but now it's known that isolation is a stress that alters brain chemistry and function.

Willy Sidis and John Stuart Mill were being stimulated and allowed to develop in one direction, but they were being isolated from interaction with their peers. When Mill was twenty he went into a depression, and later he wrote that it was because he discovered that he was unable to feel. He had developed only part of his personality.

Bertrand Russell (1872–1970), orphaned at the age of four, went to live with his grandmother, who chose not to send him to school, but provided tutors. He didn't experience a sense of academic pressure, and was able to read whatever he wanted in his late grandfather's library. He didn't realize that he was unusually bright until he went to Cambridge. The unusual freedom of his childhood must have contributed to his willingness to hold unpopular opinions. In 1916 he was fined, and in 1918 imprisoned for 6 months, for opposing the war.

In 1927, Russell and his wife, Dora Black, started a school. He later wrote that, although the average student at the school was very bright, an exceptionally bright student was likely to be ostracized by the less bright students. He commented on the harm done to the brightest students by their social isolation, probably thinking about his own education in relative isolation. A psychologist[1] has made similar observations about the isolation that can be produced by a large difference of I.Q. She did a series of studies of very bright children, beginning in 1916, including working with some of them in a program she designed in a New York public school. Her empathy allowed her to discover things that weren't apparent to her contemporaries.

During this time Lewis Terman was studying bright children, and wanted to disprove some of the popular stereotypes about intelligent people, and to support his ideology of white racial superiority. In 1922 he got a large grant, and sorted out about 1500 of the brightest children from a group of 250,000 in California. He and his associates then monitored them for the rest of their lives (described in *Genetic Studies of Genius*).

His work contradicted the stereotype of bright people as being sickly or frail, but, contrary to his expectation, there was an association between maladjustment and higher I.Q.; the incidence of neurotic fatigue, anxiety, and depression increased along with the I.Q. The least bright of his group were more successful in many ways than the most bright. He didn't really confront the implications of this, though it seriously challenged his belief in a simple genetic racial superiority of physique, intellect, and character.

I.Q. testing originated in a historical setting in which its purpose was often to establish a claim of racial superiority, or to justify sterilization or "euthanasia," or to exclude immigrants. More recently, the tests have been used to assign students to certain career paths. Because of their use by people in power to control others, the I.Q. tests have helped to create misunderstanding of the nature of intelligence. A person's "I.Q." now has very strong associations with the ideology of schooling as a road to financial success, rather than to enrichment of a shared mental life.

If a bad school resembles, on the intellectual level, a confining rat box, the educational isolation of Mill, Russell, and Sidis was emotionally limiting, almost like solitary confinement. Once when Willy Sidis was arrested for marching in a May Day parade, his father was able to keep him from going to prison, but Willy apparently would have preferred the real prison to life with his parents.

None of these three famous intellects was known for youthful playfulness, though playfulness is a quality that's closely associated with intelligence in mammals and birds. (Russell, however, in middle age developed many new interests, such as writing short stories, and had many new loves even in old age.) Stress early in life, such as isolation, reduces the playfulness of experimental animals. Playfulness is contagious, but so is the inability to play.

In schools like Summerhill, which was founded in 1921 by A. S. Neill, students aren't required to attend classes when they would rather do something else, but at graduation they usually do better on their standardized national examinations than students who have dutifully attended classes for years. For students, as for rats, freedom and variety are good for the brain, and tedious conformity is harmful. When a school is very good, it can spread a contagion of playfulness along with an interest in learning.

An environment that fosters optimal intelligence will necessarily promote the development of emotional health, and will almost certainly

foster good physical health and longevity, because no part of the physiological system can thrive at the expense of another part. And within the boundaries of life-enriching environments, there are infinite possibilities for variety.

There is a common belief in the rigidity of the adult nervous system, in analogy with feral cats or dogs, that supposedly can't be tamed if they have grown up without knowing humans. But people who have had the inclination to understand wild animals have found that, even when the animals have been captured as adults, they can become as sociable as if they had grown up in domestication. The "horse whisperer" demonstrated this sort of empathetic approach to animals. Sometimes, these people have a similar ability to communicate with people who are retarded, or autistic, or demented, but the professionalization of society has made it increasingly unlikely that people with the need for intuitive help will encounter someone who is able to give it. The closest psychology has come to professionally recognizing the importance of empathy was in Carl Rogers' work, e.g., Client-Centered Therapy.

Rogers showed that a sense of solidarity must exist between therapist and client for the therapy to be helpful. A similar solidarity has to exist between teacher and student, for education to be successful. If ordinary family and social contacts could occur within such an atmosphere of mutual respect, psychopathology (including learning difficulties) would be much less common.

Although three individuals don't prove an argument, I think the lives and situations of Sidis, Mill, and Russell are usefully symbolic. Sidis, who grew up under intense pressure and social isolation and in extreme poverty, died at the age of 46. Mill, who was educated mainly by his father, in secure financial circumstances, experienced social isolation and moderate pressure, and lived about 20 years longer than Sidis did. Russell, who grew up in the highest circles of the ruling class, experienced no pressure, and only the mild kind of social isolation that wasn't exceptional for his class. He lived to be 97.

The psychopathology of social isolation has been studied in a variety of animals, and many features are similar across species, including humans. Aggression, helplessness, and reduced ability to learn are typically produced in animals by social isolation, and it's clear that certain kinds of family environment produce the same conditions in

children. Schools seldom help, and often hinder, recovery from such early experiences.

"Vital exhaustion," decreased slow wave sleep, and anger, which are associated with the "type A personality" and with circulatory and heart disease, appear to have their origin in childhood experiences. Low income and financial insecurity are strongly associated with anger, sleep disturbances, and circulatory disease. In animals stressed by social isolation, similar features emerge, under the influence of decreased neurosteroids, and increased serotonin and activity of the glucocorticoid system.

The "smart drug" culture has generally been thinking pharmaceutically rather than biologically. Behind that pharmaceutical orientation there is sometimes the idea that the individual just isn't trying hard enough, or doesn't have quite the right genes to excel mentally.

Many stimulants—amphetamine and estrogen, for example—can increase alertness temporarily, but at the expense of long range damage. The first principle of stimulation should be to avoid a harmful activation of the catabolic stress hormones. Light, play, environmental variety and exploratory conversations stimulate the whole organism in an integral way, stimulating repair processes and developmental processes.

Any chemical support for intelligence should take into account the mind-damaging stresses that our culture can impose, and provide defense against those. In darkness and isolation, for example, the stress hormones increase, and the brain-protective steroids decrease. The memory improvement that results from taking pregnenolone or thyroid (which is needed for synthesizing pregnenolone from cholesterol) is the result of turning off the dulling and brain-dissolving stress hormones, allowing normal responsiveness to be restored.

If we know that rats nurtured in freedom, in an interesting environment, grow more intelligent, then it would seem obvious that we should experiment with similar approaches for children—if we are really interested in fostering intelligence. And since violence and mental dullness are created by the same social stresses, even the desire to reduce school violence might force the society to make some improvements that will, as a side effect, foster intelligence.

Intuitive Knowledge and Its Development

Ray Peat's Newsletter, 2009

UNDERSTANDING consciousness is necessary for understanding life. Variations of consciousness, such as dementia, depression, delusion, or insight, originality, curiosity have to be understood biologically.

To understand our ability to know and discover, I think it's valuable to consider foolishness along with wisdom, since "knowledge" consists of both. Scientists have been notorious for opposing new discoveries, but the mental rigidity of old age is so general, and well known, that many people have believed that it was caused by the death of brain cells. Individual cells do tend to become less adaptive with aging, and metabolism generally slows down with aging, but even relatively young and mentally quick people are susceptible to losing their ability to understand new ideas.

I think our use of language is both the means by which understanding can be preserved, encapsulated, and disseminated, and a great impediment to understanding. At first, words are continuous with the intuitive framework in which they are learned, but they gradually become relatively independent and abstract. Things can be learned without directly experiencing them. Even though words gradually change through use, the simple fact that they have a degree of dependability allows them to function even when there is no active thought. Uncritical listening is possible, and if a person can say something, it seems to be easy to believe that it's true. By the age of 25, our language has usually given us many assumptions about the nature of the world.

Verbal formulations of one sort are given up for new verbal formulations, in the process called education. Sometimes graduate students seem to have lost all common sense. It's as if their hard-drive had been reformatted to allow their professors to download onto it. But common sense, usually, is just what Einstein called it, an accumulation of prejudices.

Children learn language so easily that many people have seriously believed that a certain language was inherited by people of each ethnic group. Bilingual people were thought to be intellectually inferior (though it turned out that bilingualism actually increases a person's mental abilities—possibly because of the brain development known to

be produced by learning.) Eventually, people learned that the children of immigrants were as capable of learning the language of the new country as the native children were.

Then, explaining the mystery of language learning took a new form, that didn't seem foolish to most professional anthropologists and linguists. The first and most important step in the new theory was to declare that simple learning theory was inadequate to explain the development of language. Language developed, just as the silly racial theory had thought, out of our genetic endowment, except that what we inherited was now said to be a Universal Language, with its Universal Rules embedded in our chromosomes. Then, the speed with which children learn language was to be explained as the "innateness" of all of the complex stuff of language, with only a few things needing to be actually learned—those minor details that distinguish English from Eskimo or Zapotec.

Although the phrase "genetic epistemology" was coined by Jean Piaget, a major philosophical and scientific theme of the 20th century has been the idea that the "forms" of knowledge, for perceiving space, or logical relations, or language patterns, are derived from our genes, and that they are somehow built into the arrangement of our brain cells so that we spontaneously think in certain ways, and don't have the capacity to transcend the nature of our inherited brain. In that view, children have their own pre-logical way of thinking, and their thought (and language development) must proceed through certain stages, each governed by some "structural" process in the nervous system. The only thing wrong with the idea of innate knowledge is that people use it to tell us what we can't know, in other words, to rationalize stupidity. Of course, they wouldn't like to phrase it that way, because they consider their "genetic epistemology of symbolic forms" to be the essence and the totality of intelligence, and that people who allow their thoughts to be structured entirely by experience are just confused.

Years ago, I had been criticizing Noam Chomsky's theory of language so much, that I thought I might have misjudged or inappropriately depreciated his general attitude toward consciousness, so I asked him some questions about the intelligence of animals. His response confirmed my view that he subscribed to the most extreme form of "genetic epistemology":

"I don't know whether there is a common animal ability to manipulate images and generalize. In fact, I doubt it very much. Thus the kind

of 'generalization' that leads to knowledge of language from sensory experience seems to me to involve principles such as those of universal grammar as an innate property, for reasons I have explained elsewhere, and I see no reason to believe that these principles underlie generalization in other animals. Nor do I think that the kinds of generalization that lead a bird to gain knowledge of how to build a nest, or to sing its song, or to orient itself spatially, are necessarily part of the human ability to generalize."

All of the textbooks that I have seen that discuss the issue of animal intelligence have taken a position like that of Chomsky—that any knowledge animals have is either rigidly instinctual, or else is just a set of movements that have been mechanically learned. In other words, there isn't anything intelligent about the complex things that animals may do. Konrad Lorenz and the ethologists explained animal behavior in terms of chains of reflexes that are "triggered" by certain sensations or perceptions. This claim that animals' behavior just consists of mechanical chains of reflexes strictly follows Descartes' doctrine, and Chomsky has consistently acknowledged that his theory is Cartesian. The claim that children have their own non-logical way of understanding things is very similar to the doctrine about animals, in the way it limits real rational understanding to adult human beings.

The awareness of young animals is particularly impressive to me, because we know the short time they have had in which to learn about the world. Any instance in which a young animal understands a completely novel situation, in a way that is fully adequate and workable, demonstrates that it is capable of intellectual generalization.

Beyond that, I think animal inventiveness can teach us about our own capacity for inventiveness, which both the genetic and the behaviorist theories of knowledge totally fail to explain.

Spiders that build architecturally beautiful webs have been favorite subjects for theorizing about the instinctive mechanisms of behavior. When spiders were sent up on an orbiting satellite, they were in a situation that spiders had never experienced before. Spiders have always taken advantage of gravity for building their webs, and at first, the orbiting spiders made strange little muddled arrangements of filaments, but after just a few attempts, they were able to build exactly the same sort of elegant structures that spiders normally build. (My interpretation of that was that spiders may be more intelligent than most neurobiologists.)

Nesting birds often swoop at people or animals who get too close to their nest. Early last summer, I had noticed some blue jays that seemed to be acting defensive whenever I went into one part of the yard. On a very hot day at the end of summer, a couple of plump jays were squawking and apparently trying to get my attention while I was watering the front yard, and I idly wondered why they would be acting that way so late in the year. I had gone around the house to water things in the back yard, and the birds came over the house, and were still squawking, and trying to get my attention. I realized that their excitement didn't have anything to do with their nest, and looking more carefully, I saw that they were young birds. As it dawned on me that they were interested in the water squirting out of the hose, I aimed the stream up towards them, and they got as close to it as they could. Since the force of the stream might have hurt them, I put on a nozzle that made a finer spray, and the birds immediately came down to the lowest tip of the branch, where they could get the full force of the mist, holding out their wings, and leaning into the spray so that it ruffled their breast feathers. Their persistence had finally paid off when they got me to understand what they wanted, and they were enjoying the cool water. As new young birds, I don't know how they understood hoses and squirting water, but it was clear that they recognized me as a potentially intelligent being with whom they could communicate.

For a person, that wouldn't have seemed like a tremendously inventive response to the hot weather, but for young birds that hadn't been out of the nest for long, it made it clear to me that there is more inventive intelligence in the world than is apparent to most academic psychologists and ethologists.

Early porpoise researchers were surprised when a porpoise understood a sequence in which one tone was followed by two, and then by three, and answered by producing a series of four tones. The porpoise had discovered that people knew how to count.

Experiments with bees show the same sort of understanding of numbers and intentions. An experimenter set out dishes of honey in a sequence, doubling the distance each time. After the first three dishes had been found by scouts, the bees showed up at the fourth location before the honey arrived, extrapolating from the experimenter's previous behavior and inferring his intentions.

Once I noticed that an ant seemed to be dozing at the base of every maple leaf, and that there were several aphids on each leaf. I was getting very close, trying to understand why the ant was sitting so quietly. Apparently my odor gave the ant a start, and he leaped into activity, racing up the leaf, and giving each aphid a tap as he passed. When he had reached the end of the leaf and had touched every aphid, his agitation suddenly disappeared, and he returned to his spot at the base of the leaf. Although I knew that ants could count very well, as demonstrated by experiments in which an ant had to describe a complex route to a dish of honey, it was the apparent emotion that interested me. It reminded me of the hostess who counted her dishes before the guests left.

When the brains of such different kinds of animal work in such similar ways, in situations that contain many new components, I don't think it's possible to conclude anything except that intelligence is a common property of animals, and that it comprises "generalization" and much more. It's obvious that they grasp the situation in a realistic way. The situation has structured their awareness. Some people might say that they have "modeled the situation in their mind," but it's enough to say that they understand what's going on. With that understanding, motivations and intentions form part of the perception, since the situation is a developing process. Ordinarily, we say that we "infer" motivations and intentions and "deduce" probable outcomes, but that implies that the situation is static, rather than continuous with its origin and outcome. In reality, these understandings and expectations are part of the direct perception. It isn't a matter of "intelligence" operating upon "sensations," but of intelligence inhering in the grasping of the situation. (In Latin, *intelligo* meant "I perceive." I suspect that a Roman might have perceived the word intelligens as being derived from roots such as *tele-* from Greek, or *tela*, web, warp thread—and *ligo* or *lego*, connoting the binding in or gathering of what is distant or extended.)

This view of a generalized animal intelligence wouldn't seem strange, except that the history of official western philosophy, the doctrine of genetic determinism in biology, and the habits that form with the rigid uses of language, have offered another way of looking at it. The simple intelligence of an animal would disrupt all of that important stuff, so it has become mandatory to dismiss all examples of intelligent behavior by animals as "mere anthropomorphizing." Sadly, this has also meant that most intelligent behavior by humans has also been dismissed.

The cellular development of an organism used to be described as a process in which everything is predetermined by the genes, but the interactions between an embryo and its environment are now known to be crucial in shaping the process of maturation, so that the real organism (the phenotype) doesn't necessarily reflect its genetic make-up (genotype); the term "phenocopy" acknowledges this process.

London taxi drivers were recently found to have an enlargement of part of the hippocampus, compared to the brains of other people, and the difference was greater, in proportion to the time they had been driving taxis. Their brains have been shaped by their activities.

If the brain's cellular anatomy is so radically affected by activity even in adulthood, then the concept of awareness as a process in which consciousness takes its form from the situation shouldn't be problematic. If a bee and a porpoise can draw similar conclusions from similar experiences, then the world is being grasped by both in an objective way.

The environment shapes the organism's response, and the momentary response contributes to the development of the supporting processes and apparatuses. So the ability to respond is the basic question. If the richly grasped situation contains its own implications, there is no need for explaining the ability to perceive those implications in terms of some prearranged neurological code, except for the ability to respond complexly and appropriately. Any specific interpretation or behavior which is predetermined is going to function as an impediment to understanding. Verbal formulations often have the function of creating a stereotyped and inappropriate response.

The "genetic epistemologists" confuse their own verbal interpretations with the real ways that understanding develops, and when a child doesn't yet know all of the connotations of a specific word, the psychologist ascribes a pre-logical brain function to the child. The similar failure to perceive and to communicate accounts for the foolish things ethologists have said about animal intelligence.

The process in which an organism responds to a situation is continuous with the process of communication. The organism understands that in certain situations a response can be elicited, and so it acts accordingly.

Communication is a response that is directed toward eliciting a response from another. The idea that an animal might have an intention, or a desire to communicate or respond, has been obsessively denied by most official western philosophers, who see that as a uniquely human

quality, but some philosophers have even denied that quality to humans. For them, consciousness is a passive receptacle for units of meaning and logic, like a mail bin at the post-office, where letters are received, sorted, and distributed. Maybe computers work that way, but there is nothing in living substance that works like that.

Consciousness is participation, in the sense that there is a response of an organism to events. Even dreams and hallucinations have their implied reference to something real.

If a violin has been soaked in water, it will sound very odd when it's played. Its various parts won't resonate properly. Similarly, the living substance has to be in a particular state to resonate properly with its environment.

People have proposed that visual experience involves the luminescence of nerves in the optical system. Presumably, similar analogs of events could occur in various tissues when we are conscious of sounds, tastes, smells, etc. But whether or not our auditory nerves are singing when we experience music, no one questions the existence of some sort of responsive activity when we are being conscious of something. Activating certain brain areas will make us conscious of certain things, and that activation can be a response to sensory nerve impulses, or to brain chemicals produced in dreaming or drug-induced hallucinations, or to electrical stimulation, or to the act of remembering.

The history of the prefrontal leukotomy or lobotomy, in which undesirable behaviors were surgically removed, was closely associated with the development of surgical treatments for epilepsy.

Natalya Bekhtereva was exploring alternative treatments for epilepsy, implanting fine wire electrodes into the abnormal parts of the brain, and surrounding areas, to discover the nature of the electrical events that were associated with the seizures. In the process, she discovered that meanings and intentions corresponded to particular electrical patterns. She found that giving certain kinds of stimulation to healthy parts of the brain could stimulate the development of ways of functioning that bypassed the seizure-prone parts of the brain. Extending this, seeing that creating new patterns of nervous activity could overcome sickness, she proposed that creativity, the activation of the brain in new ways, would itself be therapeutic. Some people, such as Stanislav Grof, advocated the therapeutic use of LSD with a rationale that seems similar, for example to overcome chronic pain by changing its meaning, putting it into a

different relation to the rest of experience. "In general, psychedelic therapy seems to be most effective in the treatment of alcoholics, narcotic-drug addicts, depressed patients, and individuals dying of cancer." Since LSD shifts the balance away from serotonin dominance toward dopamine dominance, its effect can be to erase the habits of learned helplessness. Stress and pain also leave their residue in the endorphin system, and the anti-opiates such as naloxone can relieve depression, improve memory, and restore disturbed pituitary functions, for example leading to the restoration of menstrual rhythms interrupted by stress or aging. The amazing speed with which young animals can solve problems is undoubtedly a reflection of their metabolic vigor, and it is probably partly because they haven't yet experienced the paralysis that can result from repeated or prolonged and inescapable stress. Many of the factors responsible for the metabolic intensity of youth can be used therapeutically, even after dullness has developed. The right balance of amino acids and carbohydrates, and the avoidance of the antimetabolic unsaturated fatty acids, can make a great difference in mental functioning, even though we still don't know what the ideal formulas are.

While chemical—nutritional—hormonal approaches can help to restore creativity, the work of people like Bekhtereva shows that the exercise of creativity can help to restore biochemical and physiological systems to more normal functioning. Learning new general principles or new languages can be creatively restorative.

Iron's Dangers

Ray Peat's Newsletter, 2006

Q: You believe iron is a deadly substance. Why?

Iron is a potentially toxic heavy metal. In excess, it can cause cancer, heart disease, and other illnesses.

Q: Could you tell us about some of these studies?

In the 1960s the World Health Organization found that when iron supplements were given to anemic people in Africa, there was a great increase in the death rate from infectious diseases, especially malaria. Around the same time, research began to show that the regulation of iron is a central function of the immune system, and that this seems to have evolved because iron is a basic requirement for the survival and growth of cells of all types, including bacteria, parasites, and cancer. The pioneer researcher in the role of iron in immunity believed that an excess of dietary iron contributed to the development of leukemia and lymphatic cancers. Just like lead, mercury, cadmium, nickel and other heavy metals, stored iron produces destructive free radicals. The harmful effects of iron-produced free radicals are practically indistinguishable from those caused by exposure to X-rays and gamma rays; both accelerate the accumulation of age-pigment and other signs of aging. Excess iron is a crucial element in the transformation of stress into tissue damage by free radicals.

For about 50 years, it has been known that blood transfusions damage immunity, and excess iron has been suspected to be one of the causes for this. People who regularly donate blood, on the other hand, have often been found to be healthier than non-donors, and healthier than they were before they began donating.

In one of Hans Selye's pioneering studies, he found that he could experimentally produce a form of scleroderma (hardening of the skin) in animals by administering large doses of iron, followed by a minor stress. He could prevent the development of the condition by giving

the animals large doses of vitamin E, suggesting that the condition was produced by iron's oxidative actions.

Excess iron's role in infectious diseases is now well established, and many recent studies show that it is involved in degenerative brain diseases, such as Parkinson's, ALS (Lou Gehrig's disease), Huntington's chorea, and Alzheimer's disease. Iron is now believed to have a role in skin aging, atherosclerosis, and cataracts of the lenses of the eyes, largely through its formation of the "age pigment."

Q: How does excess iron accelerate our aging process?

During aging, our tissues tend to store an excess of iron. There is a remarkably close association between the amount of iron stored in our tissues and the risk of death from cancer, heart disease, or from all causes. This relationship between iron and death rate exists even during childhood, but the curve is downward until the age of 12, and then it rises steadily until death. The shape of this curve, representing the iron burden, is amazingly similar to the curves representing the rate of death in general, and the rate of death from cancer. There is no other relationship in biology that I know of that has this peculiar shape, with its minimum at the age of 12, and its maximum in old age at the time of death.

One of the major lines of aging research, going back to the early part of this century, was based on the accumulation of a brown material in the tissues known as "age-pigment." The technical name for this material, "lipofuscin," means "fatty brown stuff." In the 1960s, the "free radical theory" of aging was introduced by Denham Harman, and this theory has converged with the age-pigment theory, since we now know that the age-pigment is an oxidized mass of unsaturated fat and iron, formed by uncontrolled free radicals. Until a few years ago, these ideas were accepted by only a few researchers, but now practically every doctor in the country accepts that free radicals are important in the aging process. A nutrition researcher in San Diego suspected that the life-extending effects of calorie restriction might be the result of a decreased intake of toxins. He removed the toxic heavy metals from foods, and found that the animals which ate a normal amount of food lived as long as

the semi-starved animals. Recently, the iron content of food has been identified as the major life-shortening factor, rather than the calories.[1]

Q: Exactly how much iron do we need to eat?

Children's nutritional requirements are high, because they are growing, but there are indications that in the U.S. even children eat too much iron.

Some researchers are concerned that the iron added to cereals is contributing to the incidence of leukemia and cancers of the lymphatic tissues in children.[2] During the time of rapid growth, children are less likely than adults to store too much iron. At birth, they have a large amount of stored iron, and this decreases as they "grow into it." It is after puberty, when growth slows and the sex hormones are high, that the storage of iron increases.[3] In a study of the "malnourished" children of migrant fruit pickers in California, these children who were "seriously anemic" were actually more resistant to infectious diseases than were the "well nourished" middle class children in the same region.

If the normal amount of dietary iron causes an increased susceptibility to infections even in children, and if a subnormal amount of iron slows the aging process, I think we are going to have to reconsider our ideas of nutritional adequacy, to look at the long range effects of diet, as well as the immediate effects. My current studies have to do with analyzing our ability to handle stress safely, in relation to our diet. I believe our nutritional recommendations for iron have to be revised sharply downward.

Q: Don't women need extra iron?

That's a misunderstanding.

Doctors generally don't realize that only a few milligrams of iron are lost each day in menstruation. The real issue is that you can hardly avoid getting iron, even when you try.

Women absorb iron much more efficiently than men do. From a similar meal, women will normally absorb three times as much iron as men do. When pregnant, their higher estrogen levels cause them to absorb about nine times as much as men. Every time a woman menstruates, she loses a little iron, so that by the age of 50 she is likely

to have less iron stored in her tissues than a man does at the same age, but by the age of 65 women generally have as much excess iron in their tissues as men do. (During those 15 years, women seem to store iron at a faster rate than men do, probably because they have more estrogen.) At this age their risk of dying from a heart attack is the same as that of men. Some women who menstruate can donate blood regularly without showing any tendency to become anemic.

Since the custom of giving large iron supplements to pregnant women has been established, there has been an increase in jaundice of the newborn. It has been observed that women who didn't take iron supplements during pregnancy have healthy babies that don't develop jaundice. I have suggested that this could be because they haven't been poisoned by iron. Those supplements could also be a factor in the increased incidence of childhood cancer.

Q: Don't you need iron supplements if you are anemic?

In general, no. Many doctors think of anemia as necessarily indicating an iron deficiency, but that isn't correct. 100 years ago, it was customary to prescribe arsenic for anemia, and it worked to stimulate the formation of more red blood cells. The fact that arsenic, or iron, or other toxic material stimulates the formation of red blood cells doesn't indicate a "deficiency" of the toxin, but simply indicates that the body responds to a variety of harmful factors by speeding its production of blood cells. Even radiation can have this kind of stimulating effect, because growth is a natural reaction to injury. Between 1920 and 1950, it was common to think of "nutritional growth factors" as being the same as vitamins, but since then it has become common to use known toxins to stimulate the growth of farm animals, and as a result, it has been more difficult to define the essential nutrients. The optimal nutritional intake is now more often considered in terms of resistance to disease, longevity or rate of aging, and even mental ability.

An excess of iron, by destroying vitamin E and oxidizing the unsaturated fats in red blood cells, can contribute to hemolytic anemia, in which red cells are so fragile that they break down too fast. In aging, red cells break down faster, and are usually produced more slowly, increasing the tendency to become anemic, but additional iron tends to be more dangerous for older people.

Anemia in women is caused most often by a thyroid deficiency (as discussed in the chapter on thyroid), or by various nutritional deficiencies. Estrogen (even in animals that don't menstruate) causes dilution of the blood, so that it is normal for females to have lower hemoglobin than males.

Q: What should I do if my doctor tells me I'm anemic? Is there any situation in which a person needs to take iron supplements?

Iron deficiency anemia does exist, in laboratory situations and in some cases of chronic bleeding, but I believe it should be the last-suspected cause of anemia, instead of the first. It should be considered as a possible cause of anemia only when very specific blood tests show an abnormally low degree of iron saturation of certain proteins. Usually, physicians consider the amount of hemoglobin or of red cells in the blood as the primary indicator of a need for iron, but that just isn't biologically reasonable.

If a large amount of blood is lost in surgery, a temporary anemia might be produced, but even then it would be best to know whether the iron stores are really depleted before deciding whether an iron supplement would be reasonable. Liver (or even a water extract of wheat germ) can supply as much iron as would be given as a pill, and is safer.

Q: What foods contain iron?

Flour, pasta, etc., almost always contain iron which has been artificially added as ferrous sulfate, because of a federal law. Meats, grains, eggs, and vegetables naturally contain large amounts of iron. A few years ago, someone demonstrated that they could pick up a certain breakfast cereal with a magnet, because of the added iron. Black olives contain iron, which is used as a coloring material. You should look for "ferrous" or "ferric" or "iron" on the label, and avoid foods with any added iron.

Many labels list "reduced iron," meaning that iron is added in the ferrous form, which is very reactive and easily absorbed.

Q: Why does federal law require the addition of iron to those foods?

Industrially processed grains have most of the nutrients, such as vitamin E, the B vitamins, manganese, magnesium, etc., removed to improve the products' shelf life and efficiency of processing, and the government required that certain nutrients be added to them as a measure to protect the public's health, but the supplementation did not reflect the best science even when it was first made law, since food industry lobbyists managed to impose compromises that led to the use of the cheapest chemicals, rather than those that offered the greatest health benefits. For example, studies of processed animal food had demonstrated that the addition of iron (as the highly reactive form, ferrous sulfate, which happens to be cheap and easy to handle) created disease in animals, by destroying vitamins in the food. You should read the label of ingredients and avoid products that contain added iron, when possible.

Q: Can cooking in an iron frying pan put iron into food?

Yes, especially if the food is acidic, as many sauces are. The added iron will destroy vitamins in the food, besides being potentially toxic in itself.

Q: What about aluminum?

Aluminum and iron react similarly in cells and are suspected causes of Alzheimer's disease.

The aluminum industry started propagandizing more than 50 years ago about the "safety" of aluminum utensils, claiming that practically none of the toxic metal gets into the food. Recent research showed

that coffee percolated in an aluminum pot contained a large amount of dissolved aluminum, because of coffee's acidity.

Q: What kind of cooking pots or utensils are safe?

Glass utensils are safe, and certain kinds of stainless steel are safe, because their iron is relatively insoluble. Teflon-coated pans are safe unless they are chipped.

Q: How do I know which stainless steels are safe?

There are two main types of stainless steel, magnetic and nonmagnetic. The nonmagnetic form has a very high nickel content, and nickel is allergenic and carcinogenic. It is much more toxic than iron or aluminum. You can use a little "refrigerator magnet" to test your pans. The magnet will stick firmly to the safer type of pan.

Q: Why is there iron in most multi-vitamin and mineral products?

Although several researchers have demonstrated that iron destroys vitamins, there is enough wishful thinking in industry, government, and the consuming public, that such mistakes can go on for generations before anyone can mobilize the resources to bring the truth to the public. 10 years ago, I thought it was a hopeful sign of increased awareness of iron's danger when the manufacturer of a new iron product mentioned in the Physician's Desk Reference that it hadn't yet been reported to cause cancer.

Q: I can't avoid all those foods, especially the bread and grains. What can I do to keep the iron I ingest from harming me?

Iron destroys vitamin E, so vitamin E should be taken as a supplement. It shouldn't be taken at the same time as the iron-contaminated food, because iron reacts with it in the stomach. About 100 mg per day is adequate, though our requirement increases with age, as our tissue iron stores increase. Coffee, when taken with food, strongly inhibits the absorption of iron, so I always try to drink coffee with meat. Decreasing your consumption of unsaturated fats makes the iron less harmful.

Vitamin C stimulates the absorption of iron, so it might be a good idea to avoid drinking orange juice at the same meal with iron-rich foods. A deficiency of copper causes our tissues to retain an excess of iron, so foods such as shrimp and oysters which contain abundant copper should be used regularly.

Q: How does copper help us?

Copper is the crucial element for producing the color in hair and skin, for maintaining the elasticity of skin and blood vessels, for protecting against certain types of free radical, and especially for allowing us to use oxygen properly for the production of biological energy. It is also necessary for the normal functioning of certain nerve cells (substantia nigra) whose degeneration is involved in Parkinson's disease. The shape and texture of hair, as well as its color, can change in a copper deficiency. Too much iron can block our absorption of copper, and too little copper makes us store too much iron. With aging, our tissues lose copper as they store excess iron. Because of those changes, we need more vitamin E as we age.

Summary

- Iron is a potentially toxic heavy metal; an excess can cause cancer, heart disease, and other illnesses.
- Other heavy metals, including lead and aluminum, are toxic; pans and dishes should be chosen carefully.
- Iron causes cell aging.
- Drinking coffee with iron rich foods can reduce iron's toxic effects.
- Use shrimp and oysters, etc., to prevent the copper deficiency which leads to excess storage of iron.
- Avoid food supplements which contain iron.
- Take about 100 units of vitamin E daily; your vitamin E requirement increases with your iron consumption.

Glossary

Free radicals are fragments of molecules that are very destructive to all cells and system of the body.

Respiration refers to the absorption of oxygen by cells, which releases energy. The structure inside the cell in which energy is produced by respiration is called the mitochondrion. Oxidation refers to the combination of a substance with oxygen. This can be beneficial, as in normal respiration that produces energy, or harmful, as in rancidity, irradiation, or stress reactions. Antioxidants: Vitamin E and vitamin C are known as antioxidants, because they stop the harmful free-radical chain reactions which often involve oxygen, but they do not inhibit normal oxidation processes in cells. "Chain breaker" would be a more suitable term. It is often the deficiency of oxygen which unleashes the dangerous free-radical processes. Many substances can function as antioxidants/chain breakers: thyroxine, uric acid, biliverdin, selenium, iodine, vitamin A, sodium, magnesium, and lithium, and a variety of enzymes. Saturated fats work with antioxidants to block the spread of free-radical chain reactions. Age pigment is the brown material that forms spots on aging skin, and that accumulates in the lens of the eye forming cataracts, and in blood vessels causing hardening of the arteries, and in the heart and brain and other organs, causing their functions to deteriorate with age. It is made up of oxidized unsaturated oils with iron.

Anemic means lacking blood, in the sense of not having enough red blood cells or hemoglobin. It is possible to have too much iron in the blood while being anemic. Anemia in itself doesn't imply that there is nutritional need for iron.

Lactate vs. CO_2 in Wounds, Sickness, and Aging

The Other Approach to Cancer

Ray Peat's Newsletter, 2009

THE presence of lactic acid in our tissues is very meaningful, but it is normally treated as only an indicator, rather than as a cause, of biological problems. Its presence in rosacea, arthritis, heart disease, diabetes, neurological diseases and cancer has been recognized, and recently it is being recognized that suppressing it can be curative, after fifty years of denial.

The influence of politics on science is so profound that neither historians nor scientists often care to consider it honestly and in depth.

From the 19th century until the second quarter of the 20th century, cancer was investigated mainly as a metabolic problem. This work, understanding the basic chemistry of metabolism, was culminating in the 1920s in the work of Otto Warburg and Albert Szent-Györgyi on respiration. Warburg demonstrated as early as 1920 that a respiratory defect, causing aerobic glycolysis, i.e., the production of lactic acid even in the presence of oxygen, was an essential feature of cancer. (The formation of lactic acid is normal and adaptive when the supply of oxygen isn't adequate to meet energy demands, for example when running.)

Many people recognized that this was likely to be the key to the "cancer problem." But in the U.S., several factors came together to block this line of investigation.

The world wars contributed to the isolation of German scientists, and Warburg, of the famous Jewish banking family, continued his work in Germany with the support of the government, despite his open opposition to Nazism. In the years after the war, nothing positive could be said in the U.S. about his work on cancer.

The metabolic interpretation of disease that had been making progress for several decades was suddenly submerged when government research financing began concentrating on genetic and viral interpretations of disease.

If an apparently non-infectious disease couldn't be explained on the basis of an inherited tendency—insanity, epilepsy, diabetes, toxemia of pregnancy, and cancer, for example—then genetic changes occurring in the individual, as a result of chance or a virus, were invoked. Nutrition

and other conditions of life were until fairly recently said to have no influence on health if the person consumed sufficient calories and a minimum amount of the essential vitamins, minerals, and protein. The cult of genetic determinism was so powerful that it wasn't affected by the facts.

In 1932, a pediatrician, Alexis Hartmann (with M. Senn) in St. Louis, injected intravenously a solution of sodium lactate into patients with metabolic acidosis, and several of them survived—despite the fact that some of them were already suffering from an excess of lactate. The subsequent widespread use of lactate solutions in hospitals has contributed to the general denial of its toxicity.

Hartmann and Senn used racemic lactate, that is, a mixture of D-lactate and L-lactate. Our own tissues produce mostly L-lactate, but they can produce small amounts of D-lactate; larger amounts are produced by diabetics. Intestinal bacteria can produce large amounts of it, and it has many toxic effects. Methylglyoxal can be formed from either form of lactate, and it is an important factor in the glycation of proteins. It can also be formed from MDA, a product of lipid peroxidation. Protein glycation is an important factor in diabetes and aging, but glucose, rather than lactate and polyunsaturated fats, is commonly said to be the cause.

About 50 years ago, lactate was known to induce the formation of new blood vessels, and for a much longer time it has been known to cause vasodilation and edema. In 1968, it was shown to stimulate collagen synthesis.

Normally, collagen synthesis and neovascularization are caused by lack of oxygen, but lactate can cause them to occur even in the presence of oxygen. Maintenance of a normal extracellular matrix is essential for normal functioning and cellular differentiation. Abnormally stimulated collagen synthesis probably accelerates tumor growth.[1]

Nervous and hormonal factors can cause lactate to accumulate, even without prior damage to the mitochondria.[2] Psychological, as well as physical, stress and overactivation of glutamate receptors can cause harmful accumulation of lactate in the brain.[3] Rather than just being "associated with" tissue damage, lactate directly contributes to the damage, for example in the brain, causing nerve cell loss by increasing the release of excitotoxic glutamate.[4] When a panic reaction is produced by sodium lactate, the reduction of protective neurosteroids appears

to contribute to the excitatory state;[5] this would make the brain more susceptible to damage.

Lactate increases blood viscosity, mimics stress, causes inflammation, and contributes to shock. Lactated Ringer's solution contributes to the tissue damage caused by shock, when it's used to resuscitate shock victims:[6,7] it contributes to the inflammatory processes associated with shock, unlike the use of hypertonic saline and other solutions. Lactate contributes to diabetes, inhibiting the ability to oxidize glucose. It promotes endothelial cell migration and leakiness, with increased vascular permeability factor (VPF or vascular endothelial growth factor, VEGF):[8] this can lead to breakdown of the "blood-brain barrier."

In the brain, lactate can cause nerve damage, increasing intracellular fat accumulation, chromatin clumping, and mitochondrial swelling.[9]

The lactate in peritoneal dialysis solution impairs differentiation and maturation of (immune, monocyte derived) dendritic cells; according to the authors of the study, "These findings have important implications for the initiation of immune responses under high lactate conditions, such as those occurring within tumor tissues or after macrophage activation."[10]

Lactate also causes macrophages and synovial fibroblasts to release PGE_2, which can contribute to inflammation and bone resorption.[11] This is the prostaglandin known to activate the formation of estrogen.[12]

Hartmann's lactated solution has been widely used in hospitals for resuscitation and for patients after heart surgery and other stressful procedures, but until recently only a few people have objected to its use, and most of the objection has been to the use of racemic lactate, rather than to lactate itself. In recent years several studies have compared hypertonic saline (lacking the minerals considered essential since Sydney Ringer formulated his solution around 1885), and have found it in some cases superior to the "balanced" lactate solution. Even hypertonic glucose, without minerals, has produced good results in some studies.

A solution containing a large amount of lactate has been used for peritoneal dialysis when there is kidney failure, but several studies have compared solutions using bicarbonate instead of lactate, and found that they don't cause the severe damage that always happened with the traditional solution.

While Warburg was investigating the roles of glycolysis and respiration in cancer, a physician with a background in chemistry, W.F. Koch, in Detroit, was showing that the ability to use oxygen made the difference

between health and sickness, and that the cancer metabolism could be corrected by restoring the efficient use of oxygen. He argued that a respiratory defect was responsible for immunodeficiency, allergy, and defective function of muscles, nerves, and secretory cells, as well as cancer. Koch's idea of cancer's metabolic cause and its curability directly challenged the doctrine of the genetic irreversibility of cancer that was central to governmental and commercial medical commitments.

Albert Szent-Györgyi respected Koch's work, and spent years investigating the involvement of the lactate metabolites, methylgyoxal and glyoxal, in cell physiology, but since the government's campaign against Koch was still active when Szent-Györgyi came to the U.S., he worked out many of the implications of Koch's work relating to cellular oxidation without mentioning his name.

Lactate formation from glucose is increased when anything interferes with respiratory energy production, but lactate, through a variety of mechanisms, can itself suppress cellular respiration. (This has been called the Crabtree effect.) Lactate can also inhibit its own formation, slowing glycolysis. In the healthy cell, the mitochondrion keeps glycolysis working by consuming pyruvate and electrons (or "hydrogens") from NADH, keeping the cell highly oxidized, with a ratio of NAD^+/NADH of about 200. When the mitochondrion's ability to consume pyruvate and NADH is limited, the pyruvate itself accepts the hydrogen from NADH, forming lactic acid and NAD^+ in the process. As long as lactate leaves the cell as fast as it forms, glycolysis will provide ATP to allow the cell to survive. Oxygen and pyruvate are normally "electron sinks," regenerating the NAD^+ needed to produce energy from glucose.

But if too much lactate is present, slowing glycolytic production of ATP, the cell with defective respiration will die unless an alternative electron sink is available. The synthesis of fatty acids is such a sink, if electrons (hydrogens) can be transferred from NADH to $NADP^+$, forming NADPH, which is the reducing substance required for turning carbohydrates and pyruvate and amino acids into fats.

This transfer can be activated by the transhydrogenase enzymes in the mitochondria, and also by interactions of some dehydrogenase enzymes.

The enzyme, fatty acid synthase (FAS), normally active in the liver and fat cells and in the estrogen-stimulated uterus, is highly active in cancers, and its activity is an inverse indicator of prognosis. Inhibiting it

can cause cancer cells to die, so the pharmaceutical industry is looking for drugs that can safely inhibit it. This enzyme is closely associated with the rate of cell proliferation, and its activity is increased by both cortisol and estrogen.

The first biochemical event when a cell responds to estrogen is the synthesis of fat. Estrogen can activate transhydrogenases, and early studies of estrogen's biological effects provided considerable evidence that its actions were the result of the steroid molecule's direct participation in hydrogen transfers, oxidations and reductions. E.V. Jensen's claim that estrogen acts only through a "receptor protein" which activated gene transcription was based on his experimental evidence indicating that estrogen doesn't participate in oxidation and reduction processes in the uterus, but subsequently his claim has turned out to be false.

Glycolysis is very inefficient for producing usable energy compared to the respiratory metabolism of the mitochondria, and when lactate is carried to the liver, its conversion to glucose adds to the energy drain on the organism.

The hypoglycemia and related events resulting from accelerated glycolysis provide a stimulus for increased activity of the adaptive hormones, including cortisol. Cortisol helps to maintain blood sugar by increasing the conversion of protein to amino acids, and mobilizing free fatty acids from fat stores. The free fatty acids inhibit the use of glucose, so the stress metabolism relies largely on the consumption of amino acids. This increases the formation of ammonia, yet the combination of glycolysis and fat oxidation provides less carbon dioxide, which is needed for the conversion of ammonia to urea. Ammonia stimulates the formation of lactate, while carbon dioxide inhibits it.

Starving an animal with a tumor increases the stress hormones, providing free fatty acids and amino acids, and accelerates the tumor's growth;[13] it's impossible to "starve a tumor," by the methods often used. Preventing the excessive breakdown of protein and reducing the release of fatty acids from fat cells would probably cause many cancer cells to die, despite the availability of glucose, because of lactate's toxic effects, combined with the energy deficit caused by the respiratory defect that causes their aerobic glycolysis. Recently, the intrinsically high rate of cell death in tumors has been recognized. The tumor is maintained and enlarged by the recruitment of "stem cells." These cells normally

would repair or regenerate the tissue, but under the existing metabolic conditions, they fail to differentiate properly.

The extracellular matrix in the tumor is abnormal, as well as the metabolites and signal substances being produced there, and the new cells fail to receive the instructions needed to restore the normal functions to the damaged tissue. These abnormal conditions can cause abnormal differentiation, and this cellular state is likely to involve chemical modification of proteins, including remodeling of the chromosomes through acetylation of the histones.[14,15] The protein-protective effects of carbon dioxide are replaced by the protein-damaging effects of lactate and its metabolites.

The ability of lactic acid to displace carbon dioxide is probably involved in its effects on the blood clotting system. It contributes to disseminated intravascular coagulation and consumption coagulopathy, and increases the tendency of red cells to aggregate, forming "blood sludge," and makes red cells more rigid, increasing the viscosity of blood and impairing circulation in the small vessels.[16–19]

The features of the stress metabolism include increases of stress hormones, lactate, ammonia, free fatty acids, and fat synthesis, and a decrease in carbon dioxide. Factors that lower the stress hormones, increase carbon dioxide, and help to lower the circulating free fatty acids, lactate, and ammonia, include vitamin B_1 (to increase CO_2 and reduce lactate), niacinamide (to reduce free fatty acids), sugar (to reduce cortisol, adrenaline, and free fatty acids), salt (to lower adrenaline), thyroid hormone (to increase CO_2). Vitamins D, K, B_6 and biotin are also closely involved with carbon dioxide metabolism. Biotin deficiency can cause aerobic glycolysis with increased fat synthesis.[20]

A protein deficiency, possibly by increasing cortisol, is likely to contribute to increased FAS and fat synthesis,[21] but the dietary protein shouldn't provide an excess of tryptophan, because of tryptophan's role as serotonin precursor—serotonin increases inflammation and glycolysis.[22]

Incidental stresses, such as strenuous exercise combined with fasting (e.g., running or working before eating breakfast) not only directly trigger the production of lactate and ammonia, they also are likely to increase the absorption of bacterial endotoxin from the intestine. Endotoxin is a ubiquitous and chronic stressor. It increases lactate and nitric oxide, poisoning mitochondrial respiration, precipitating the secretion of the

adaptive stress hormones, which don't always fully repair the cellular damage.

Aspirin protects cells in many ways, interrupting excitotoxic processes by blocking nitric oxide and prostaglandins, and consequently it inhibits cell proliferation, and in some cases inhibits glycolysis, but the fact that it can inhibit FAS[23] is very important in understanding its role in cancer.

There are several specific signals produced by lactate that can promote growth and other features of cancer, and it happens that aspirin antagonizes those: HIF, NF-κB, the kinase cascades, cyclin D_1, and heme oxygenase.

Lactate and inflammation promote each other in a vicious cycle.[24]

The toxic mechanism of bacterial endotoxin (lipopolysaccharide) involves inappropriate stimulation[25] of cells, followed by inflammation and mitochondrial inhibition. The stimulation seems to be a direct "biophysical" action on cells, causing them to take up water,[26] which is especially interesting, since estrogen's immediate excitatory effect causes cells to take up water.

Hypoosmolarity itself is excitatory and anabolic. It stimulates lipolysis and fat oxidation,[27] and osmotic swelling stimulates glycolysis and inhibits mitochondrial respiration.[28] Endotoxin causes hyponatremia,[29] and a hypertonic salt solution is protective, lactate solutions are harmful. Other stresses and inflammations also cause hyponatremia.

One of the effects of endotoxin that leads to prolonged cellular excitation is its inhibition of the glucuronidation system,[30] since this inhibition allows excitatory estrogen to accumulate.

In women and rats, antibiotics were found to cause blood levels of estrogen and cortisol to decrease, while progesterone increased. This effect apparently resulted from the liver's increased ability to inactivate estrogen and to maintain blood sugar when the endotoxin stress was decreased.

Now that hog farmers' use of antibiotics to stimulate growth has been discouraged, they have sought vegetables that have a natural antibiotic effect, reducing the formation and absorption of the intestinal toxins. The human diet can be similarly adjusted, to minimize the production and absorption of the bacterial toxins.

In 2007, two Canadian researchers announced that they were investigating the drug dichloroacetate, which blocks glycolysis, stopping the

production of lactic acid, as a cancer treatment, with success. The drug (dichloroacetate) has toxic side effects, but it is useful in several other conditions involving over-production of lactic acid. Other drugs that inhibit glycolysis have also shown anticancer effects in animals, but are in themselves very toxic. On the theoretical level, it would be better to inhibit only aerobic glycolysis, rather than inhibiting enzymes that are essential for all glycolysis.

Since endotoxemia can produce aerobic glycolysis in an otherwise healthy person,[31] a minimally "Warburgian" approach—i.e, a merely reasonable approach—would involve minimizing the absorption of endotoxin. Inhibiting bacterial growth, while optimizing intestinal resistance, would have no harmful side effects. Preventing excessive sympathetic nervous activity and maintaining the intestine's energy production can be achieved by optimizing hormones and nutrition. Something as simple as a grated carrot with salt and vinegar can produce major changes in bowel health, reducing endotoxin absorption, and restoring constructive hormonal functions.

Medical tradition and inertia make it unlikely that the connection between cancer and bowel toxins will be recognized by the mainstream of medicine and government. In another article I will describe some of the recent history relating to this issue.

It's nice that some cancer researchers are now remembering Warburg, but unfortunately they are usually just fitting the fact of cancer's aerobic glycolysis into the genetic mutant cell paradigm, thinking of the respiratory defect as just another opportunity for killing the evil deviant cancer cell, rather than looking for the causes of the respiratory defect. Warburg, Koch, and Szent-Györgyi had a comprehensive view of biology, in which the aerobic production of lactate, resulting from a respiratory defect, itself was functionally related to the nature of cancer.

A focus on correcting the respiratory defect would be relevant for all of the diseases and conditions (including heart disease, diabetes, dementia) involving inflammation and inappropriate excitation, not just for cancer.

Glossary

Aerobic glycolysis, the conversion of glucose to lactic acid even in the presence of oxygen. The presence of oxygen normally restrains glycolysis so that glucose is converted to carbon dioxide instead of lactic acid.

Anaerobic glycolysis, the increased conversion of glucose to lactic acid when the supply of oxygen isn't sufficient, which is a normal event during intense muscle action.

"Warburg Effect" refers to Otto Warburg's observation that cancer cells produce lactic acid even in the presence of adequate oxygen. Cancer cells don't "live on glucose," since they are highly adapted to survive on protein and fats.

Pasteur Effect, the normal response of cells to restrain glycolysis in the presence of adequate oxygen.

Crabtree Effect, observed originally in yeast, refers to the inhibition of respiration in the presence of glucose. This occurs in cancers[32] and in rapidly proliferating normal cells.[33]

"Cancer metabolism" or stress metabolism typically involves an excess of the adaptive hormones, resulting from an imbalance of the demands made on the organism and the resources available to the organism. Excessive stimulation depletes glucose and produces lactic acid, and causes cortisol to increase, causing a shift to the consumption of fat and protein rather than glucose. Increased cortisol activates the Randle effect (the inhibition of glucose oxidation by free fatty acids), accelerates the breakdown of protein into amino acids, and activates the enzyme fatty acid synthase, which produces fatty acids from amino acids and pyruvate, to be oxidized in a "futile cycle," producing heat, and increasing the liberation of ammonia from the amino acids. Ammonia suppresses respiratory, and stimulates glycolytic, activity.

Leakiness, Aging, and Cancer

Ray Peat's Newsletter, 2006

A thin layer of fibrin lining blood vessels provides a filtering barrier that helps to strengthen the wall and prevent other proteins from leaking out of the vessels, and it participates in repair processes when the blood vessel is broken.

Cellular energy metabolism is the basis for maintaining the barrier functions. Energy depletion causes the endothelial cells lining blood vessels to become excessively permeable.

When the organism's resistance is low, proteins and fats that normally remain inside the bloodstream can escape into the extracellular matrix and enter cells, contributing to their stress and disorganization, and other materials can escape from cells and enter the bloodstream.

One of the simplest demonstrations of fibrin leakage is to shine a beam of light into the eye; the presence of fibrin and other inappropriate molecules diffuses the light, causing a "flare" in the aqueous compartment. Albumin, a small protein from the blood, is often seen in the urine during stress. The effects of that sort of leakage vary with each organ.

Fibrin is an essential structural and functional part of the organism, but when it escapes from the bloodstream it participates in the degenerative processes of inflammation, fibrosis, and tumor formation. (Its fragments stimulate secretion of inflammatory mediators: Hamaguchi et al., 1991.)

In the hormonal environment dominated by estrogen, mild stresses such as exertion, or even restless sleep, allow toxins (and sometimes bacteria) from the intestine to enter the bloodstream, triggering a complex chain of events that create a systemic inflammatory state. Although these processes have been observed in many simple experiments, their implications are almost always neglected or denied or explained away. Incorporation of certain polyunsaturated fats into the tissues increases the leakiness of blood vessels, and amplifies the reactions to stresses and inflammatory stimuli.

Antioxidants, thyroid hormone, progesterone, and antiinflammatory agents, including glycine or gelatin, niacin, and saturated fats, can prevent, and in many cases reverse, these degenerative inflammatory processes.

Even a single celled organism has to keep its parts separate, and highly differentiated multicelled organisms have many special systems that serve to keep their parts separate, so the different tissues and organs can maintain their distinct functions.

The movement of substances from blood to cell, and from cell to cell, is normally very tightly controlled, and when the systems that control those movements of water and its solutes are damaged, the tissues' structures and functions are altered. The prevention of inappropriate leakiness can protect against the degenerative processes, and against aging itself, which is, among other things, a state of generalized leakiness.

When cells' energy is depleted, water and various dissolved molecules are allowed to move into the cells, out of the cells, and through or around cells inappropriately. The weakened cells can even permit whole bacteria and similar particles to pass into and out of the blood stream more easily.

One of the earliest investigators of the effects of stress and fatigue on nerves and other cells was A.P. Nasonov, in the first half of the 20th century. A.S. Troshin (1956) has reviewed his work in detail. He showed that in cells as different as algae and nerve cells, fatigue caused them to take up dyes, and that the dyes were extruded, if the cells were able to recover their energy. When nerve cells are excited for a fraction of a second, they take up sodium and calcium, but quickly eliminate them. Prolonged excitation, leading to fatigue, can gradually shift the balance, allowing more substances to enter, and to stay longer.

When nerves or other cells are quickly killed with heavy metals such as osmium, the metals are visible in a layer at the surface, which is sometimes taken as evidence of a "cytoplasmic membrane," but if the cells have suffered oxygen deprivation or have been injured by X-rays, the metal will be visible as a grey color evenly distributed through the cell. The deposition of the metal occurs when it reacts with electrons. In the relatively vital cell, the heavy metal stops at the surface, and is mostly reduced there, but the devitalized cell presents no structural or chemical barrier to the entry of the metal, and the reactive electrons appear to be evenly distributed through the cell. Oxygen deprivation, X-irradiation, and other stresses cause the cell to be unable to use electrons to produce energy, and instead the electrons are available to react destructively with whatever may be available. While Nasonov showed that dyes and even particles enter energetically depleted cells, newer techniques are able

to show that the leaky cells are structurally disrupted by the excessive reduction of their proteins, by excited electrons and free radicals.

In the 1970s, experimenters found that muscles from vitamin E-deficient animals released their enzymes when washed in a saline solution, more easily than did the muscles from vitamin E replete animals. Other experiments around the same time showed that reducing the ATP of muscles caused a similar loss of their ability to retain their proteins.

Over the years, many experiments have established, both *in vitro* and in vivo, that fatigue, stress, aging, and inflammation cause cells to lose their normal constituents, but also to allow foreign materials to enter more easily.

When I was working on my thesis, around 1970, investigating the effects of aging on the metabolism of the uterus, I found that the changes occurring during aging were (in all the ways I tested) the same as those produced by X-irradiation, excess estrogen, oxygen deprivation, excess polyunsaturated fats, and vitamin E deficiency.

Although everyone working in the lab was familiar with the appearance of the uterus from old hamsters (they are typically large, stiff, and bluish), everyone was surprised when I suggested that the aged uteri seemed to function as if they were under the influence of a considerable amount of estrogen. Everyone was familiar with the medical textbook doctrine that "menopause is caused by estrogen deficiency." In humans, gynecologists know about "Chadwick's sign," the fact that the uterine cervix turns blue or purple during pregnancy, and everyone knows that blood is blue when it's deprived of oxygen, so it's surprising that estrogen's effect on tissue oxygenation isn't widely recognized.

When estrogen is given to an animal, it almost instantly causes capillaries to become leaky, allowing water to move out of the blood stream, and at the same time, estrogen causes cells to take up water. Both of these processes are the same as the early effects of oxygen deprivation. In the normal reproductive cycle, the surge of estrogen lasts only a few hours, and normal permeability is quickly restored by increasing progesterone. During those intermittent short exposures to estrogen, there isn't a massive leakage of serum proteins into the tissues. During the time of estrogenic influence, all kinds of cells are influenced, with the excitatory equilibrium of nerve cells, glandular cells, and immune system cells being shifted, lowering the threshold of excitation, or prolonging the excited state.

Anything that causes inflammation causes a similar loss of water from the blood, as it is taken up by swelling cells. If inflammation is generalized, it causes circulatory shock, because the volume of the blood has become insufficient to serve the organism's needs. One of Hans Selye's earliest observations of the effect of an overdose of estrogen was that it causes shock.

Although water loss causes the blood to become more viscous under the influence of estrogen, the plasma becomes hypotonic, meaning that it contains fewer osmotically active solutes than normal; some of the sodium that helps to maintain the blood's osmotic balance is lost through the kidneys, and some is taken up by the red blood cells and other cells. The osmotic imbalance of the blood causes tissue cells to take up more water, contributing to their increased excitability. In many cases, the vascular leakage of inflammation and shock can be corrected by using osmotically active substances, such as starch solutions, gelatin, or concentrated sodium chloride.

The tissue water retention caused by estrogen, hypoxia, and stress is analogous to the swelling of gels and colloids, that is, it's governed by the state of the electrons and counterions in the system. Excitation, fatigue, or injury can cause a shift of pH toward alkalinity, causing water uptake and swelling.

The blue color of the pregnant cervix, or of the uterus in an animal given an overdose of estrogen, indicates that the tissue isn't sufficiently oxygenated to maintain its normal red color, even though the flow of blood is increased. Some experimenters have noticed that newborn animals sometimes have the postural reflex (lordosis) that indicates an estrogenic state, and that suffocation can produce the same reflex. Irradiating animals with x-rays will also produce the whole range of estrogenic effects.

One of the features of the aged uterus that I studied was the age pigment, lipofuscin, a brown waxy material that accumulates in old or stressed tissues. Prolonged dosage with estrogen accelerates the formation of this pigment, which is largely derived from oxidized polyunsaturated fatty acids. Increased amounts of those fats in the diet, or a deficiency of vitamin E, or exposure to ionizing radiation, or oxygen deprivation, can also accelerate the formation of the age pigment. The presence of the pigment intensifies the effect of estrogen, since the pigment wastes oxygen by functioning as an oxidase enzyme.

Other tests that I did on aged, or estrogenized, uterine tissue indicated that several oxidative systems were activated; for example, the tissues showed an extremely high activity of the enzyme peroxidase, and a very intense reduction of a chemical dye (tetrazolium/formazan) that indicates the presence of reductive and oxidative activity, of the sorts caused by radiation and oxygen deprivation. These reductive and oxidative processes include the production of some free radicals that are capable of reacting randomly with polyunsaturated fatty acids.

The interactions between estrogen and the polyunsaturated fats are now coming to be more widely recognized as important factors in the inflammatory/hyperpermeable conditions that contribute to the development of heart and blood vessel disease, hypertension, cancer, autoimmune diseases, dementia, and other less common degenerative conditions.

Estrogen increases lipid peroxidation, and maintains a chronically high circulating level of free fatty acids, mainly PUFA, activates the phospholipases that release arachidonic acid from cells leading to formation of prostaglandins and isoprostanes, and increases the enzymes that form the inflammation-promoting platelet activating factor (PAF) while suppressing the enzymes that destroy it, and increases a broad range of other inflammatory mediators, interleukins, and NF-kappa B.

The leakage of enzymes out of cells and into the blood stream is recognized medically as evidence of damage to the organ that is losing them. Different combinations of enzymes are commonly considered to be evidence of a heart attack, or skeletal muscle damage, or liver disease, pancreatitis, prostate cancer, etc. But often the reason for the leakage isn't understood. Hypothyroidism, for example, causes leakage of enzymes, possibly mainly from the liver, but also from other organs. Excess estrogen, intense exercise, starvation, anything that increases lipid peroxidation and free radical production, such as drinking alcohol when the tissues contain polyunsaturated fats, can cause organs such as heart and liver to leak their components.

The loss of enzymes increases the energy needed to stay alive, but it doesn't necessarily change the basic functions of the cell. (Though when mitochondrial enzymes leak out into the cytoplasm, the cell's energy metabolism is impaired, at least temporarily.) But the entry of catalytic materials from other tissues changes the organization of a cell, giving it conflicting instructions. In many situations, as L.V. Polezhaev

and V. Filatov demonstrated, the substances released during stress and degeneration serve to stimulate healing and regeneration. But when the resources aren't available for full repair or regeneration, only a scar, or atrophic fibrosis, or a tumor will be formed.

In severe stress, intracellular fibrin deposits have been found in the heart and other organs, including the prostate gland. Deficiency of testosterone causes vascular leakage into the prostate. Fibrin promotes tumor growth, partly by serving as a matrix, partly by releasing stimulatory peptides.

Kidney disease, diabetes, pregnancy toxemia and retinal degeneration are probably the best known problems involving vascular leakage, but increasingly, cancer and heart disease are being recognized as consequences of prolonged permeability defects. Congestive heart failure and pulmonary hypertension commonly cause leakage of fluid into the lungs, and shock of any sort causes the lung to get "wet," a waterlogged condition called "shock lung." Simply hyperventilating for a couple of minutes will increase leakage from the blood into the lungs; hyperventilation decreases carbon dioxide, and increases serotonin and histamine. Hyperoxia itself contributes to lung injury, and exacerbates emphysema, though it is common to see patients breathing a high concentration of oxygen. Emphysema (which can be caused by hypothyroidism or hyperestrogenism, and often can be cured by thyroid or progesterone) and many other respiratory problems are associated with capillary leakage. Cells of the lung and intestine are able to synthesize their own fibrin, apparently because of their special problems in preventing leakage. Prolonged systemic inflammation can lead to lung fibrosis, and fibrosis increases the likelihood of lung cancer.

The inflammatory state that causes exaggerated cellular permeability is very closely related to "hyperventilation," the loss of too much carbon dioxide. The release of serotonin during hyperventilation isn't the only cause of vascular leakage; the carbon dioxide itself is an essential factor in regulating the state of cellular electrons and in maintaining cellular integrity. Hyperventilation, like the shift from oxidative to glycolytic energy production that typifies estrogenized or stressed cells or cancer, raises intracellular pH. In the case of mast cells, increasing alkalinity causes them to release histamine (Alfonso, et al., 2005), but similar "alkaline-induced exocytosis" seems to occur in all stressed tissues.

The blood platelets that become incontinent and leak serotonin in the absence of carbon dioxide are undergoing the same structural stresses experience by endothelial cells, smooth muscle cells, mast cells and all other cells when carbon dioxide is depleted. Although it has been about 70 years since Yandell Henderson made it clear that supplemental oxygen should be combined with carbon dioxide, mechanical ventilation in hospitals is still causing lung injury resulting from hyperventilation, i.e., the absence of carbon dioxide. A similar misunderstanding of biology was involved in the use of dialysis to treat kidney disease. Until recently, commercial dialysis fluids contained acetate and/or racemic lactate instead of bicarbonate, because of the difficulty of preparing bicarbonate solutions, and the result was that very prolonged dialysis would damage the brain and other organs. (Veech and Gitomer, 1988, Veech and Fowler, 1987.) Dialysis has been seen to increase lung permeability (Bell, et al., 1988).

Amyloidosis produced by chronic dialysis affects all organs, but its effects are best known in the brain, heart, kidneys, and lungs. Serum amyloid-A is one of the acute phase proteins, like C-reactive protein (CRP), that are produced by inflammation. Estrogen, radiation and other stresses increase those pro-inflammatory acute phase proteins, and decrease protective albumin, which is called a "negative acute phase protein," since it decreases when the other acute phase proteins increase. The liver is the major source of the acute phase proteins, and it is constantly burdened by toxins absorbed from the bowel; disinfection of the bowel is known to accelerate recovery from stress.

Seen from the perspective of the stress-leakage syndrome, any serious injury or sickness damages all organs. The exhaled breath is being used to diagnose inflammatory lung disease, since so many of the mediators of inflammation are volatile, but systemic diseases such as cancer and arthritis, and relatively minor stress can be detected by changes in the chemicals found in the breath. Polyunsaturated fats and their breakdown products—aldehydes, prostaglandins, isoprostanes, hydrocarbons, and free radicals—and carbon monoxide, nitric oxide, nitrite, and hydrogen peroxide are increased in the breath by most stresses. Both proline and glycine (which are major amino acids in gelatin) are very protective for the liver, increasing albumin, and stopping oxidative damage.

Saturated fats are protective against free radical damage and can reverse liver fibrosis. Thyroid hormone protects against excess estrogen,

and can prevent or reverse fibrosis of the heart. Antiestrogens are widely effective against vascular leakage. Thyroid, progesterone, and testosterone are among the most effective natural antiestrogens, and they are curative in many conditions that involve vascular leakage. Progesterone and pregnenolone have been called the antifibromatic steroids, and it has been used to treat many inflammatory and fibrotic diseases, including cancer.

The antiserotonin drugs are being increasingly used to treat fibrotic diseases, and other problems related to vascular leakage.

Antiinflammatory and anticoagulant things, especially aspirin and vitamin E, protect against the accelerated turnover of fibrinogen/fibrin caused by estrogen and the various inflammatory states.

Meat Physiology, Stress, and Degenerative Physiology

Ray Peat's Newsletter, 2014

THE U.S. Department of Agriculture claims that the Pure Food and Drugs Act of 1906 and the Meat Inspection Act of the same year were passed because the food industry demanded them. Ordinary historians believe that Upton Sinclair's 1905 serial publication of his novel about the meat industry, The Jungle, caused the public and Theodore Roosevelt to pressure Congress to pass the laws. Sinclair's descriptions of the use of poisonous preservatives and deodorants to disguise the smell of rotten meat angered the public and the president enough to overcome the industry pressure that had kept the US Congress from regulating the commercial food supply long after European governments had begun regulating food production and sales.

Before the government's intervention, it was common practice to soak all kinds of meat in water or chemical solutions to increase their weight. At present, the U.S. Department of Agriculture, through the mass media and funding the training of food technologists and "meat scientists," now takes the position that it is natural for meat to leak water after it is packaged, and says it is perfectly legal for meat producers to soak the meat in water with chemicals until it has increased its weight by 8 %. The chemicals, such as trisodium phosphate (in a solution strength as high as 12 %), are chosen because they powerfully stimulate swelling and water retention. Considerable amounts of some chemicals, such as sodium citrate, are allowed to add to the weight of the meat. The use of ozone and hydrogen peroxide to deodorize meat causes instantaneous oxidative changes, including lipid peroxidation and protein carbonyl formation, as well as increasing water retention.

Most supermarket meat is now packaged with thick diapers so the buyer won't notice that he is paying for a sizeable amount of pink water. The USDA has an internet site, and consumer hotlines, to inform angry consumers that they are mistaken if they believe that meat shouldn't leak. They explain that meat is now "bred" to contain less fat, and so it contains more water, and that it is simply the leanness of the meat that accounts for its poor flavor.

Before the slaughtered animal is put into the soaking solution to gain a specific amount of weight, the animal has almost always been treated in ways that cause it to go to slaughter in a state of massive edema. Even before the meat is soaked, the animal has been treated to maximize its water retention.

Muscle physiologists and endocrine physiologists know that fatigue, stress and excess estrogen can cause the tissues to swell hugely, increasing their weight and water content without increasing their protein content.

As soon as cheap synthetic estrogens, such as DES, became available in the 1940s, their use in animals was promoted because it was clear that they caused massive water retention. Women who suffer from hyperestrogenism always have a problem with water retention, but they have never been known to suffer from over-developed skeletal muscles. In fact, in humans of both sexes, an excess of estrogen has been commonly associated with sarcopenia, muscular dystrophy, and atrophy of the skeletal muscles. Similar observations have been made in a variety of animals. Meat scientists are the only people I know of who have ever referred to estrogen as an anabolic steroid, in the sense of "building muscle."

When it was publicized around 1970 that DES is powerfully carcinogenic, after it had been used for several decades in the meat industry, its use was outlawed, but its illegal use continued and was overlooked by the U.S. government. The Swiss government has rejected meat from a large producer in Kansas because it contained DES. Other estrogens are openly used, and the U.S. government continues to apply pressure to other countries to accept meat exports containing estrogens.

There are many ways to increase the water content of meat, besides feeding estrogen to the animal and soaking the meat after slaughter. Everything that causes water retention and tissue swelling in the living animal, that is, every kind of stress, fatigue, poisoning, malnutrition and injury, will make the animal gain weight, without consuming expensive nutritious food. Crowding, fright, and other suffering increase water retention and accelerate the breakdown of fats and proteins.

The water content of meat shouldn't be increased by any of those methods, not only because it is a form of stealing from the consumer, but because it makes the product toxic and unappetizing, and makes the production process a degrading experience.

Any chemicals, such as estrogen or arsenic, that remain in the meat are of course harmful to the consumer, but the changes they produce in the animals' tissues are the main problem. When grains and soybeans are used for fattening animals, their characteristic fatty acids are present in the meat, and are harmful to the consumer, but their complex degradation products, such as isoprene, acrolein, and isoprostanes, remain, along with the complex changes they induce in every aspect of the tissue. The reactive products of oxidative fat degradation stimulate, among other things, the adaptive/defensive production of polyamines, small molecules derived from amino acids. The polyamines, in turn, can be oxidized, producing highly toxic aldehydes, including acrolein.[1] These molecules stimulate cell multiplication, and alter, at least temporarily, the way the cell's genes function.

An excess of water stimulates cell division, and an important mechanism in producing that effect is the increased production of polyamines by the enzyme ornithine decarboxylase. This enzyme is activated by an excess of water (hypotonicity), by estrogen, and by stress.

Besides stimulating cell division and modifying the cell's state of differentiation (including developmental imprinting), the polyamines also contribute to nerve cell excitation and excitotoxicity. Estrogen and excess water can contribute to nerve cell excitation, for example producing convulsive seizures. The polyamines are increased during seizures, and they can affect the stability of the nerve cells, for example contributing to cocaine's seizure-sensitizing action. Although they tend to block free radicals, they accelerate nerve injury,[2] and can contribute to breakdown of the blood-brain barrier.[3,4]

The polyamines are increased in cancers, and therapies to block their formation are able to stop the growth of various cancers, including prostate, bowel, and breast cancer. Metabolites of the polyamines in the urine appear to be useful as indicators of cancer and other diseases. (In pancreatic cancer,[5] in cervical cancer,[6] and in adult respiratory stress syndrome.[7]) The quantity of polyamines in the urine of cancer patients has been reported to be 20 times higher than normal.[8] Polyamines in the red blood cells appear to indicate prognosis in prostate cancer.[9]

The prostaglandins in semen have been suspected to have a role in producing cervical cancer.[10]

In protein catabolism, one fate of the protein's nitrogen is to be converted to the polyamines, rather than to urea. In plants, at least, these small molecules help cells to balance osmotic stresses.

Adding water to meat, or stressing the animals before slaughter, will increase the meat's content of the polyamines, but the longer the meat is stored, the greater will be the production of reactive oxygen products and polyamines.

The deliberate "aging" of meat is something that the meat scientists often write about, but it has a peculiar history, and is practiced mainly in the English speaking cultures. When a supermarket in Mexico City began selling U.S.-style meat for the American colony, I got some T-bone steaks and cooked them for some of my Mexican friends. The meat wasn't water-logged (it was 1962, and the beef had been grown in Mexico), but it had been aged for the American customers, and though my friends ate the steaks for the sake of politeness, I could see that they found it difficult.

In Mexico, even in the present century, butcher shops often don't have refrigeration, and they don't need it because they sell the meat immediately. The fresh meat tastes fresh. Traditionally, liver is sold only on the day of slaughter, because its high enzyme content causes it to degrade much faster than the muscle meats. When it is fresh, it lacks the characteristic bad taste of liver in the U.S.

Both the liver and the muscles contain a significant amount of glycogen when they are fresh, if the animal was healthy. At first, the lack of oxygen causes the glycogen to be metabolized into lactic acid, and some fatty acids are liberated from their bound form, producing slight changes in the taste of the meat. But when the glycogen has been depleted, the anaerobic metabolism accelerates the breakdown of proteins and amino acids.

In the absence of oxygen, no carbon dioxide is produced, and the result is that the normal disposition of ammonia from amino acids as urea is blocked, and the polyamines are formed instead. The chemical names of two of the main poly-amines are suggestive of the flavors that they impart to the aging meat: Cadaverine and putrescine. After two or three weeks of aging, there has been extensive breakdown of proteins and fats, with the production of very complex new mixtures of chemicals.

Mexicans, despite their low average income, have a very high per capita consumption of meat, as do several other Latin American coun-

tries. Argentina has a per capita meat consumption of nearly a pound a day. There is a lot of theorizing about the role of meat in causing cancer, for example comparing Japan's low mortality from prostate cancer, and their low meat consumption, with the high prostate cancer mortality in the U.S., which has a higher meat consumption. But Argentina and Mexico's prostate cancer mortality ranks very favorably with Japan's.

If meat consumption in the U.S. contributes to the very high cancer rate, it clearly isn't the quantity of meat consumed, but rather the quality of the meat.

The polar explorer Vilhjalmur Stefansson was interested in the health effects of a diet based on meat, because of his observation that fresh meat prevented scurvy much more effectively than the fruits and vegetables carried by other polar explorers. He commented on the importance of culture and learning in shaping food preferences:

"In midwinter it occurred to me to philosophize that in our own and foreign lands taste for a mild cheese is somewhat plebeian; it is at least a semi-truth that connoisseurs like their cheeses progressively stronger. The grading applies to meats, as in England where it is common among nobility and gentry to like game and pheasant so high that the average Midwestern American or even Englishman of a lower class, would call them rotten."

"I knew of course that, while it is good form to eat decayed milk products and decayed game, it is very bad form to eat decayed fish. I knew also that the view of our populace that there are likely to be 'ptomaines' in decaying fish and in the plebeian meats; but it struck me as an improbable extension of the class-consciousness that ptomaines would avoid the gentleman's food and attack that of a commoner."

"These thoughts led to a summarizing query; If it is almost a mark of social distinction to be able to eat strong cheeses with a straight face and smelly birds with relish, why is it necessarily a low taste to be fond of decaying fish? On that basis of philosophy, though with several qualms, I tried the rotten fish one day, and if memory serves, liked it better than my first taste of Camembert. During the next weeks I became fond of rotten fish."

Since Stefansson's observations nearly a century ago, most Americans have become accustomed to the taste of half-spoiled meat, as part of the process of adapting to an industrial-commercial food system. Tests done by food technologists have found that most Americans prefer the

taste of synthetic strawberry flavor in ice cream to the taste of ice cream made with real strawberries. If it took Stefansson only a few weeks to become fond of rotten fish, it isn't surprising that the public would, over a period of many decades, learn to enjoy a diet of stale foods and imitation foods.

Polyamines are increased in stressed and stored vegetables, as in aged meats. This defensive reaction retards tissue aging, and researchers are testing the application of polyamines to fruits to retard their ripening. A plastic surgeon, Vladimir Filatov, discovered that tissue stored in the cold stimulated the healing process when used for tissue reconstruction, such as corneal transplants. He found that stressed plant tissues developed the same tissue stimulants. Another pioneer of tissue transplantation, L. V. Polezhaev, saw that degenerating tissue produced factors that seem to activate stem cells.

Although the diffusion of these stimulating factors from stressed tissues normally functions to accelerate healing and tissue regeneration, under less optimal conditions they are undoubtedly important factors in tissue degeneration and tumor formation. For example, the bystander effect (contributing to delayed radiation damage, and producing a field of precancerous changes around a cancer), in which substances diffusing from injured tissues damage surrounding cells, involves disturbances in polyamine metabolism.

The direct, optimal effects of the polyamines are protective, but when excessive, prolonged, or without maintained cellular energy, they become harmful.

The expression of genes involves their physical arrangement and accessibility to enzymes and substrates. The negatively charged nucleic acids are associated with positively charge proteins, the histones. The very small positively charged polyamines can powerfully modify the interactions between histones and DNA. In recent years people have begun to speak of the "histone code," as a kind of expansion of the idea of the "genetic code." But the polyamines, produced in response to stress, might be thought of as a complex expansion of the "histone code."

The addition of small molecules, methyl and acetyl groups, to the large molecules can regulate the expression of genes, and these patterns can be passed on transgenerationally, or modified by stress. Barbara McClintock's "controlling factors" were mobile genes that caused the genome to be restructured under the influence of stress. Her discov-

eries were the same as those made by Trofim Lysenko decades earlier, and like his observations, McClintock's were angrily rejected until the 1980s, when the genetic engineering industry needed some scientific background and natural precedent for their unnatural intervention in the genome.

The brain is extremely different from a malignant tumor, and the derangements produced by stress, by high cortisol and estrogen and an excess of water, are different in the two types of organ (considering the tumor as an *ad hoc* organ), but the polyamines have central roles in the degenerating brain and in the divergent disorganization of tumors. Their importance in stress physiology is coming to be recognized, along with the meaning of "epigenetic development," in which the influence of the environment becomes central, rather than just a place in which the "genotype" is allowed to passively express its "genetic potential." Every developmental decision involves an evaluation of resources and their optimal marshaling for adaptation. The polyamines are part of the cytoplasm's equipment for controlling the genome. The ratio between the different types of polyamine governs the nature of their regulation of cellular functions.

The old idea, "one is what one eats," has evolved far beyond ideas of simple nutritional adequacy or deprivation, and it's now commonly accepted that many things in foods have fairly direct effects on our brain transmitters and hormones, such as serotonin, dopamine, adrenalin, endorphins, prostaglandins, and other chemicals that affect our behavior and physiology.

In 1957 James McConnell discovered that when flatworms were fed other flatworms that had been trained, their performance was improved by 50 %, compared with normal flatworms. Later, similar experiments were done with rats and fish, showing that tissue extracts from trained animals modified the behavior of the untrained animals so that it approximated that of the trained animals. Georges Ungar, who did many experiments with higher animals, demonstrated changes in brain RNA associated with learning, and he and McConnell believed that proteins and peptides were likely to be the type of substance that transmitted the learning.

A dogmatic belief that "memory molecules" would be unable to penetrate the "blood-brain barrier" allowed most biologists to dismiss their work. Ungar's death, and the hostility of most biologists to their

work, have caused their ideas to be nearly forgotten for the last 30 years. Negatively charged molecules such as ordinary proteins tend to be repelled by negative charges on the wall of capillaries, but positively charged molecules spontaneously associate with cellular proteins, and easily penetrate the barrier. Highly positively charged molecules tend to concentrate in the brain,[11] and people are currently attempting to use the principle to deliver antibodies (which are normally excluded from the brain) therapeutically to the brain by combining them with small positively charged molecules.[12] This affinity of the brain for positively charged molecules is gradually being recognized as an important factor in the toxicity of ammonia and guanidine derivatives. As mentioned earlier, even endogenous polyamines can be involved in disruption of the blood-brain barrier.

So, apart from the question of exactly what molecules were responsible for the learning transfer produced by McConnell and Ungar, there should be no doubt that polyamines derived from food can enter tissues, especially the brain. People who eat meat from stressed animals are substantially replicating the experiments of McConnell and Ungar, except that people normally eat a variety of foods, and each type of food will have had slightly different experiences in its last days of life. But the deliberate aging of meat is subjecting it to a standardized stress—two or three weeks of cold storage. Because of the great generality of genetic processes, it wouldn't be surprising if cold storage of vegetables turned out to produce polyamine patterns similar to those of cold storage meats. Air pollution and other stressful growing conditions cause vegetables to have very high levels of polyamines.

Prolonged exposure to certain patterns of polyamines might produce particular syndromes, but the mere fact of increasing the total quantity of polyamines in our diet is likely to increase the incidence of stress-related diseases. Experiments with cells in culture show that added polyamines can produce a variety of extremely harmful changes, but so far, there has been almost no investigation of their specific regulatory functions, of their "code."

Besides rejecting stale foods produced under stressful conditions, there are probably some specific ways that we can protect ourselves from polyamine poisoning.

When the organism is functioning efficiently, its respiration is producing an abundance of carbon dioxide, which protectively modifies

many systems and structures. Adequate carbon dioxide protects against fatigue, cellular and vascular leakiness, edema and swelling.

Increasing carbon dioxide will tend to direct ammonia into urea synthesis, and away from the formation of polyamines. Bicarbonate protects against many of the toxic effects of ammonia, and since carbon dioxide spontaneously reacts with amino groups, it probably helps to inactivate exogenous polyamines. This could account for some of the protective effects of carbon dioxide (or high altitude), for example its anti-seizure, anticancer, and antistress effects.

Other things that protect against excessive polyamines are procaine and other local anesthetics,[13] magnesium, niacin, vitamin A, aspirin, and, in some circumstances, caffeine. Since endotoxin stimulates the formation of polyamines, a diet that doesn't irritate the intestine is important. Tryptophan and methionine contribute to the formation of polyamines, so gelatin, which lacks those amino acids and is soothing to the intestine, should be a regular part of the diet.

Because the polyamines intensify the neurotoxic and carcinogenic effects of estrogen and of polyunsaturated fats, those three types of substance should be considered as a functional unit in making food choices. (Grass-fed organic beef fresh from a local farm would be a reasonable choice.) Unfortunately, the meat industry has maximized all of those dangers, just for the increased weight of their product.

Membranes, Plasma Membranes, and Surfaces

Ray Peat's Newsletter, 2009

TWICE, editors have printed my articles on unsaturated fats, with adjoining "rebuttals," but I was disappointed that all of my points were ignored, as if you could rebut an argument by just saying that you emphatically disagree with it. I think it is evident that those people don't know what would be involved in refuting an argument. They are annoyed that I have bothered them with some evidence, but not sufficiently annoyed to cause them to try to marshal some evidence against my arguments.

Marketing and medical claims are intertwined with a view of life that permeates our culture. I am aware that my criticism of the doctrine of the essentiality of linoleic acid threatens the large profits of many people, and threatens the prestige of the most popular "theory of cell structure," but I think it is important to point out that nutritional and medical advice depend on the truth of the theory of cell structure and function which supports that advice, and so it is reasonable to see how sound that theory is.

As I understand it, the doctrine of the "essential fatty acids" goes this way:

- They are essential because they are required for making cell membranes and prostaglandins.
- Rats deprived of the unsaturated fatty acids develop a skin disease, and "lose water" through the skin.
- Human skin diseases (etc.) can be cured with polyunsaturated fats.

In fact, rats may get a skin disease when fed a fat-free diet, but the observation that vitamin B_6 cures it should have laid to rest the issue of

The "essential fatty acids":
Suppress metabolism and promote obesity; are immunosuppressive; cause inflammation and shock; are required for alcoholic liver cirrhosis; sensitize to radiation damage; accelerate formation of aging pigment, cataracts, retinal degeneration; promote free radical damage and excitoxicity; cause cancer and accelerate its growth; are toxic to the heart muscle and promote atherosclerosis; can cause brain edema, diabetes, excessive vascular permeability, precocious puberty, progesterone deficiency...

the dietary essentiality of the polyunsaturated oils more than 50 years ago. Scientifically, it did, but forces greater than science have revivified the monster. Experiments that confirm the disproof are done periodically—animals living generation after generation without unsaturated oils in their diet or any evidence of harm, human cells growing in culture-dishes without polyunsaturated fats, for example—without noticeable effect on the doctrine, which is perpetuated in many effective, nonscientific ways—textbooks, advertisements, college courses, for example.

Now, instead of demonstrating harm from a dietary lack of the "essential" fats, the presence of the Mead acid or omega-9 fatty acids is taken as evidence of a deficiency. Our cells (and animal cells) produce these unsaturated fats when their special desaturase enzymes are not suppressed by the presence of exogenous linoleic or linolenic acids. Normally, the inactivation of an enzyme system and the suppression of a natural biological process might be taken as evidence of toxicity of the vegetable oils, but here, the occurrence of the natural process is taken as evidence of a deficiency. To me, this seems very much like the "disease" of having tonsils, an appendix, or a foreskin—if it is there, you have a problem, according to the aggressive surgical mentality. But what is the "problem" in the case of the natural Mead or omega-9 acids? (I think the "problem" is simply that they allow us to live at a higher energy level, with greater resistance to stress, better immunity, and quicker healing.)

There have been arguments based on "membranes" and on prostaglandins. The absence of "good" prostaglandins would seem to be an obvious problem, except that the "good" prostaglandins always turn out to have some seriously bad effects when examined in other contexts. Animals that lack dietary unsaturated fats appear to escape most of the problems that are associated with prostaglandins, and I think this means that many of the toxic effects of the unsaturated vegetable oils result from the quantity and type of "eicosanoid"/lipoxygenase products made from them.

One type of membrane argument had to do with the fragility of red blood cells, reasoning, apparently, that the cells are "held together" by a lipid bilayer membrane. (Just what is the tensile strength of a lipid bilayer? Why do fatty acids or saponins weaken blood cells, instead of reinforcing them? If the "tensile strength" of a lipid layer exists, and is positive rather than negative, it is negligible in relation to the tensile strength of the cytoplasm.) Another type of :"membrane" argument

was that the mitochondria are abnormal when animals don't get the essential fatty acids in their diet, because the mitochondria are supposed to be essentially membranous structures containing the essential fatty acids. (Actually, the deficient mitochondria produce more ATP than do mitochondria from animals fed the vegetable oils.) Another argument is that "membrane fluidity" is a good thing, and that unsaturated essential fatty acids make the membranes more fluid and thus better—by analogy with their lower bulk-phase melting temperature. (But the measure of fluidity is a very limited thing on the molecular level, and this fluidity may be associated with decreased cellular function, instead of the postulated increase.)

The most addled sort of argument about "membranes" is that animals on the diet lacking polyunsaturated oils have skin that is unable to retain water because of "defective cell membranes." The skin's actual barrier function is the result of multiple layers of keratinized ("cornified," horny) cells, which have become specialized by their massive production of the protein keratin—very much as red blood cells become specialized by producing the protein, hemoglobin. Since these cells lose most of their water as they become horny, the issue of whether they still have a "plasma membrane" seems to have little interest to researchers; the same can be said regarding the cells of hair and nails. After the epidermal cells have become keratinized and inert, the sebaceous glands in the skin secrete oils, which are absorbed by the dense, proteinaceous cells, causing increased resistance to water absorption. The ideas of a plasma membrane on the cell, and of the water-barrier function of the skin, are two distinct things, that have been blurred together in a thoughtless way. It has been suggested that vitamin B_6 cures the characteristic skin disorder of a vitamin B_6 deficiency by altering fat metabolism, but the vitamin is involved in cell division and many other processes that affect the skin.

Given the fact that the "essential" oils aren't essential for the growth of cells, they can't be essential for making plasma membranes (if cells must have plasma membranes), or mitochondrial membranes, or any kind of membrane, but as long as there is the idea that fats mainly have the function of building membranes, someone is going to argue that membranes containing vegetable oils are more fluid, or more youthful, or more sensitive, or better in some way than those containing Mead acids, palmitic acid, oleic acid, stearic acid, etc.

For over a century, people have suggested that cells are enclosed in an oily membrane, because there are higher or lower concentrations of many water-soluble substances inside cells, than in the blood, lymph, and other extracellular fluids, and the idea of a membrane was invoked[1–3] to explain how that difference can persist. (By 1904, the idea of a membrane largely made of lecithin was made ludicrous by A. Nathansohn's observation that water-soaked lecithin loses its oily property, and becomes very hydrophilic; the membrane was supposed to exclude water-soluble molecules while admitting oil-soluble molecules.)

Inside the cell membrane, the cell substance was seen as a watery solution. Biochemistry, as a profession, was strongly based on the assumption that, when a tissue is ground up in water, the dilute extract closely reflects the conditions that existed in the living cell. Around 1970, when I tried to talk to biochemists about ways to study the chemistry of cells that would more closely reflected the living state, a typical response was that the idea was ridiculous, because it questioned the existence of biochemistry itself as a meaningful science. But since then, there has been a progressive recognition that organization is more important in the life of a cell than had been recognized by traditional biochemistry. Still, many biochemists thoughtlessly identify the chemistry of the living cell with their study of the water-soluble enzymes, and relegate the insoluble residue of the cell to "membrane-associated proteins" or, less traditionally, to "structural proteins." It has been several decades since the structural/contractile protein of muscle was found to be an enzyme, an ATPase, but the idea that the cell itself is a sort of watery solution, in which the water-soluble enzymes float, randomly mingling with dissolved salts, sugars, etc., persists, and makes the idea of a semipermeable membrane seem necessary, to separate a "watery internal phase" from the watery external phase. Physical chemists have no trouble with the fact that a moist protein can absorb oil as well as water, and the concept that even water-soluble enzymes have oil-loving interiors is well established. If that physical-chemical information had existed in Overton's time, there would have been no urge to postulate an oily membrane around cells, to allow substances to pass into them, in proportion to their solubility in oil.

Because biochemists like to study their enzymes in watery test-tube solutions, they find it easy to think of the cell-substance as a watery solution. With that belief, it is natural that they prefer to think of the

primeval ocean as where life originated. Their definitions of chemical reactions and equilibria in the water-phase (and by extension in cells) ignore the alternative reactions and equilibria that would occur in an environment in which ordinary water was not the dominant medium. By this failure to consider the alternatives, they have created some problems that are hard to explain. For example, the polymerization of amino acids into protein is energetically expensive in water, but it is spontaneous in a relatively dry environment, and this spontaneous reaction creates non-random structures with the capacity for building larger structures, with stainable bilayer "membranes," and with catalytic action.[4] Similarly, the problem of ATP synthesis essentially disappears when it is considered in an environment that controls water. The scientific basis for the origin of life in a "primeval soup" never really existed, and more people are now expressing their scepticism. However, biochemists have their commitments:

"In the course of biological evolution, one of the first developments must have been an oily membrane that enclosed the water-soluble molecules of the primitive cell, segregating them and allowing them to accumulate to relatively high concentrations. The molecules and ions contained within a living organism differ in kind and in concentration from those in the organism's surrounding." (Principles of Biochemistry, supposedly by Lehninger, Nelson, and Cox, though Lehninger is dead and I think his name is attached to it to exploit his fame.[†] Worth Publishers, 1993.)

Hair is composed of thoroughly dead cells, but if it is washed until it contains no sodium or potassium, and then dipped in serum, or a solution of sodium and potassium, it takes up much more potassium than sodium, in the way a living cell does, concentrating potassium "against the gradient." That is the sort of behavior that led to the postulation of a plasma membrane, to maintain the organization that was created by expending energy. "Membrane pumps" use energy, supposedly, to establish the concentration difference, and the barrier membrane keeps the solutes from diffusing away. The lipid bilayer membrane was an early guess, and the pumps were added later, as needed. Gilbert Ling reviewed the published studies on the various "membrane pumps," and found that the energy needed to operate them was 15 times greater than all the energy the cell could possibly produce.

Water softeners contain an ion-exchange resin, that uses the same principle hair does to concentrate ions, which is simply a selectivity based on the acidity of the resin, and the size of the ion. The resin binds calcium more strongly than it binds sodium, and so the water gives up its calcium in exchange for sodium.[†] Gilbert Ling devised many experiments that demonstrated the passivity of ion-accumulation by living cells.

Usually, cells are surrounded by and imbedded in materials that they have secreted, and their surfaces are often covered with materials that, while remaining anchored to the cell, have a considerable affinity for water. Physically, many of the molecules attached to cells are "surfactants," making the cell wettable, though it isn't customary to describe them as such. The glycoproteins that give cells their characteristic immunological properties are among these materials. At a certain point, there is a transition between the "outside" of the cell, which is relatively passive and water-friendly, and the cell itself, in which water is subordinated to the special conditions of the cell. (The postulated lipid bilayer membrane, in contrast, has two phase discontinuities, one where it meets the cytoplasm, another where it meets the outside world.) At this phase boundary, between two different substances, it is normal to find an electrical potential difference. When two electrically different substances are in contact, it isn't surprising to find an electrical double-layer at the surface. This is a passive process, which doesn't take any energy to maintain, but it can account for specific arrangements of molecules in the region of the phase boundary, since they are exposed to the electrical force of the electrical double-layer. That is to say that in a completely inert and homogeneous substance, a "surface structure" will be generated, as a result of the electrical difference between that substance and the adjoining substance. (This surface structure, if it is to be described as a membrane, must be called a "wet membrane," while the lipid bilayer would be a "dry membrane," since exclusion of water is its reason for existing.) Too many biologists still talk about "electrogenic membrane pumps," indicating that they haven't assimilated the results of Gilbert Ling's research.

To say it another way, there are several kinds of physical process that will govern the behavior of fats, and fats of different types will interact in different ways with their environments. They interact complexly with

their environment, serving in many cases as regulatory signal-substances. To describe their role as "membranes" is worse than useless.

Cells can be treated with solvents to remove practically all fats, yet the cells can still show their characteristic membranes: Plasma membrane, mitochondrial membranes, even the myelin figures. The proteins that remain after the extraction of the fats appear to govern the structure of the cell.

A small drop of water can float for a moment on the surface of water; this is explained in terms of the organization of the water molecules near the surface. No membrane is needed to explain this reluctance to coalesce, even though water has a very high affinity for water.

People believed in the "lipid bilayer membrane" for decades before the electron microscope was able to produce an image that could be said to correspond to that theoretical structure. Osmic acid, which is believed to stain fats, does produce a double layer at the surface of cells. However, the arrangement of fat molecules in the lipid bilayer is such that the fatty tails of the two layers are touching each other, while their acidic heads are pointed away from each other. A lipid bilayer, in other words, contains a single zone of fat, bounded by two layers of acid. The "fat-staining" property of osmic acid, then, argues against the lipid bilayer structure.

Osmic acid is very easily reduced electrically, forming a black product. Proteins with their sulfur molecules in a reduced state, for example, would cause an osmium compound to be deposited, and the appearance of two layers of osmium at the cell's phase boundary would be compatible with the idea of an electrical double-layer, induced in proteins.

Electrically charged proteins, which are able to interact with glutathione to increase or decrease their degree of reduction/electrical charge, distributed throughout the cytoplasm, would explain another feature of osmic acid staining, which is incompatible with the "fat-staining" concept. Asphyxia increases the stainability of cells with osmic acid, and this change seems to represent the availability of electrons, rather than the distribution of fats, since the change can appear within 3 minutes. (C. Peracchia and J. D. Robertson, "Increase in osmiophilia of axonal membranes of crayfish as a result of electrical stimulation, asphyxia, or treatment with reducing agents," J. Cell Biol. 51, 223, 1971; N. N. Bogolepov, Ultrastructure of the Brain in Hypoxia, Mir, Moscow, 1983) The amino groups of proteins might also be stained by osmic acid,

though asphyxia would more directly affect the disulfide groups. The increased staining with silver in asphyxia similarly suggests an increase in sulfhydryls.

Freezing cells, and then fracturing them and coating the fragments with metal or carbon is often used to "demonstrate the lipid bilayer," so it is interesting that the osmium compound that "reveals" the lipid bilayer for the electron microscope destroys the apparent membrane in the freezing technique. (R. James and D. Branton, "The correlation between the saturation of membrane fatty acids and the presence of membrane fracture faces after osmium fixation," Biochim. Biophys. Acta 233, 504-512, 1971; M. V. Nermut and B. J. Ward, "Effect of fixatives on fracture plane in red blood cells," J. Microsc. 102, 29-39, 1974.)

So, when someone says "we need the essential fatty acids to make cell membranes," my response is likely to be "no, we don't, and life probably originated on hot lava and has never needed lipid membranes."

On the third argument, that vegetable oils can be used therapeutically, I am likely to say yes, they do have some drug-like actions, for example, linseed oil has been used as a purgative, but as with any drug you should make sure that the side effects are going to be acceptable to you. Currently, it is popular to recommend polyunsaturated oils to treat eczema and psoriasis. These oils are immunosuppressive, so it is reasonable to think that there might be some pleasant consequences if a certain immunological process is suppressed, but they are also intimately involved with inflammation, sensitivity to ultraviolet light, and many other undesirable things. The traditional use of coal tar and ultraviolet light was helpful in suppressing eczema and psoriasis, but its tendency to cause cancer has led many people to forego its benefits to protect their health.

If you want to use a polyunsaturated oil as a drug, it is worthwhile to remember that the "essential fatty acids" suppress metabolism and promote obesity; are immunosuppressive; cause inflammation and shock; are required for alcoholic liver cirrhosis; sensitize to radiation damage; accelerate formation of aging pigment, cataracts, retinal degeneration; promote free radical damage and excitoxicity; cause cancer and accelerate its growth; are toxic to the heart muscle and promote atherosclerosis; can cause brain edema, diabetes, excessive vascular permeability, precocious puberty, progesterone deficiency, skin wrinkling and other signs of aging.

Whether any of the claimed pharmaceutical uses of the polyunsaturated oils, besides purgation, turn out to be scientifically valid remains to be seen. The theoretical bases often used to back up the claimed benefits are confused or false, or both.

People who are willing to question the validity of an "orthodox method," such as the glass microelectrode, are in a position to make observations that were "forbidden" by the method and its surrounding ideology.[5] Their perception is freed in ways that could lead to new understanding and practical solutions to old problems.

But sometimes experiments seem to be designed as advertising, rather than science. Recent studies of the effects of fish oils on night vision or development of the retina, for example, seem to forget that fish oil contains vitamin A, and that vitamin A has the effects that are being ascribed to the unsaturated fatty acids.

With the financial cutbacks in university libraries, there is a risk that the giant seed-oil organizations will succeed in using governmental power to regulate the alternative communication of scientific information, allowing them to control both public and "scientific" opinion more completely than they do now.

† In their preface, Nelson and Cox say their book has retained "Lehninger's groundbreaking organization, in which a discussion of biomolecules is followed by metabolism and then information pathways," but that at every other level "this second edition is a re-creation, rather than a revision, of the original text. Every chapter has been comprehensively overhauled, not just by adding and deleting information, but by completely reorganizing its presentation and content…" This is reminiscent of the book published under the name of Max Gerson after his death, which inserted essentially fraudulent material to support an approach that is exactly what Gerson strongly advised against.

† This principle might be applicable to the removal of calcium from living cells, with a procedure that wouldn't have the dangers of chelation. Increased consumption of sodium and magnesium should facilitate the removal and excretion of abnormally retained calcium. Sodium has been found to protect tissues against oxidative damage, for example during cancer therapy with cis-platinum.

Menopause and Its Causes

Ray Peat's Newsletter, 2006

WHEN I was in graduate school at the University of Oregon, everyone in our lab was working on the problem of reproductive aging. Previously, people in the lab had established that the ovaries didn't "run out of eggs." There was never really any basis for that ridiculous belief. Many people just said it, the way they said "old eggs" (but never old sperms) were responsible for birth defects, or that "estrogen is the female hormone," a deficiency of which is the cause of menopausal infertility. (Old sperms have been implicated in some birth defects. People who are newly married, for example, were found to have children with fewer birth defects than people of the same age who had been married a long time, suggesting that more frequent intercourse involves fresher sperms.) When ovaries have been treated with x-rays to destroy their ability to ovulate, they have been found to produce more estrogen than before. Ovulation is one thing, and the production of hormones is another thing. You can't determine whether ovulation has occurred by measuring the hormones.

Knowing the large amount of work that has gone into our understanding of the age-related decline in fertility, it is disturbing to see people on television and in popular health books saying that menopause occurs when the "ovaries run out of eggs."

Around 1970, many people were saying that aging was caused by the loss of brain cells. There is a glimmer of truth in that silly idea, just as there would be in saying that "aging is caused by the death of skin cells," making the skin thinner and drier and less elastic. Both the brain and the skin are sources of steroid hormones, and it is possible that the death of skin cells and neurons is one factor in the age-related decline in the "sex steroids." An organism would be an easier thing to understand if cells just did their job for a certain period of time, and then died. A man named Hayflick has given people some publications to cite, when they want to simplify things by saying that aging occurs when cells have used up their quota of 50 divisions, but there are many more studies that clearly show that Hayflick's limit is nothing but a product of the cells' environment. The cell's environment, the signals and substances and energy it receives, is complex, but real progress is

being made in understanding the things involved in the aging process. Luckily, the infinite complexity of the environment is channeled into an understandable array of processes by the cell's systematic ways of responding.

I knew, from talking with L. C. Strong, that early reproductive maturity was associated with early death; in his strains of cancer-prone mice, he showed that high estrogen was the cause of early puberty, a high cancer incidence, and a relatively short life. D. A. Snowdon, et al., showed that the occurrence of menopause at an early age in women is associated with a greater risk of death from all causes, including strokes and coronary heart disease. (They saw ovarian aging as an indicator of general aging.) P. W. F. Wilson, et al., reported that postmenopausal estrogen use was associated with an increased incidence of heart disease and stroke. P. M. Wise showed that estrogen accelerates aging of the central nervous system, destroying the nerves which regulate the pituitary gonadotropins, and causing ovarian failure and infertility. Many other studies of particular tissues show that estrogen accelerates the rate of aging.

In my work with hamsters, I found that the infertility that developed at middle age was caused by a high rate of oxygen consumption in the uterus, causing the oxygen needed by the developing embryo to be consumed by uterine tissues, and causing suffocation of the embryo. This is the central mechanism by which the estrogen-containing contraceptives work: at any stage of pregnancy, a sufficient dose of estrogen kills the embryo.

Polvani and Nencioni, among others, found that in women, the onset of menopause (the first missed period, suddenly increased bone loss, nervous symptoms such as depression, insomnia, and flushing) corresponds to the failure to produce progesterone, while estrogen is produced at normal levels. This results in a great functional excess of estrogen, because it is no longer opposed by progesterone. Typically, it takes about four years for the monthly estrogen excess to disappear. They suggested that the bone loss sets in immediately when progesterone fails because cortisol then is able to dominate, causing bone catabolism; progesterone normally protects against cortisol. Other researchers have pointed out that estrogen dominance promotes mitosis of the prolactin-secreting cells of the pituitary, and that prolactin causes osteoporosis; by age 50, most people have some degree of tumefaction of the prolactin-

secreting part of the pituitary. But estrogen dominance (or progesterone deficiency) also clearly obstructs thyroid secretion, and thyroid governs the rate of bone metabolism and repair. Correcting the thyroid and progesterone should take care of the cortisol/prolactin/osteo- porosis problem.

P. M. Wise has demonstrated that the "menopausal" pituitary hormones, high levels of LH and FSH, are produced because the regulatory nerves in the hypothalamus have lost their sensitivity to estrogen, not because estrogen is deficient. In fact, he showed that the nerves are desensitized precisely by their cumulative exposure to estrogen. If an animal's ovaries are removed when it is young, the regulatory nerves do not atrophy, and if ovaries are transplanted into these animals at the normally infertile age, they are fertile. But if animals are given larger doses of estrogen during youth, those nerves atrophy prematurely, and they become prematurely infertile.

The mechanism by which estrogen desensitizes and kills brain cells is now recognized as the "excitotoxic" process, in which the excitatory transmitter glutamic acid is allowed to exhaust the nerve cells. (This explains the older observations that glutamic acid, or aspartic acid, or aspartame, can cause brain damage and reproductive failure.) Cortisol also activates the excitotoxic system, in other brain cells, causing stress-induced atrophy of those cells. Progesterone and pregnenolone are recognized as inhibitors of this excitotoxic process.

Besides estrogen's promotion of excitotoxic cell death, leading to the failure of the gonadotropin regulatory system, estrogen's stress-mimicking action probably tends to increase the secretion of LH, in ways that can be corrected by supplementing progesterone and thyroid. Since Selye's work, it has been known that estrogen creates the same conditions as occur in the shock phase of the stress reaction. (And shock, in a potential vicious circle, can increase the level of estrogen.) It has recently been demonstrated that estrogen stimulates the adrenal glands, independently of the pituitary's ACTH. This can increase the production of adrenal androgens, leading to hirsutism, and other male traits, including anabolic effects.

It was established in the 1950s that estrogen "erases" memories in well trained animals. I suppose that acute effect is related to the chronic toxicity that leads to cell death. (In the 1940s, DES was sold to prevent miscarriages, though it was already known that it caused

them; then there was the argument that it slowed aging of the skin, despite the Revlon studies at the University of Pennsylvania showing that it accelerates all aspects of skin aging; lately there has been talk of promoting estrogen to improve memory.)

Estrogen's nerve-exciting action is known to lower seizure thresholds; premenstrual epilepsy is probably another acute sign of the neurotoxicity of estrogen.

When fatigue and lethargy are associated with aging, the brain stimulating action of estrogen can make a woman feel that she has more energy. (Large doses given to rats will make them run compulsively; running wheels with odometers have shown that they will run over 30 miles a day from the influence of estrogen.) Estrogen inhibits one of the enzymic routes for inactivating brain amines, and so it has more general effects on the brain than just the glutamate system. This generalized effect on brain amines is more like the effects of cocaine or amphetamine. If that is a woman's basis for wanting to use estrogen, a monoamine oxidase inhibitor would be safer.

The reason for the menopausal progesterone deficiency is a complex of stress-related causes. Free-radicals (for example, from iron in the corpus luteum) interfere with progesterone synthesis, as do prolactin, ACTH, estrogen, cortisol, carotene, and an imbalance of gonadotropins. A deficiency of thyroid, vitamin A, and LDL-cholesterol can also prevent the synthesis of progesterone. Several of the things which cause early puberty and high estrogen, also tend to work against progesterone synthesis. The effect of an intra-uterine irritant is to signal the ovary to suppress progesterone production, to prevent pregnancy while there is a problem in the uterus. The logic by which ACTH suppresses progesterone synthesis is similar, to prevent pregnancy during stress. Since progesterone and pregnenolone protect brain cells against the excitotoxins, anything that chronically lowers the body's progesterone level tends to accelerate the estrogen-induced excitotoxic death of brain cells.

Since progesterone and pregnenolone protect brain cells against the excitotoxins, anything that chronically lowers the body's progesterone level tends to accelerate the estrogen-induced excitotoxic death of brain cells.

Chronic constipation, and anxiety which decreases blood circulation in the intestine, can increase the liver's exposure to endotoxin. Endotoxin (like intense physical activity) causes the estrogen concentration of the

blood to rise. Diets that speed intestinal peristalsis might be expected to postpone menopause. Penicillin treatment, probably by lowering endotoxin production, is known to decrease estrogen and cortisone, while increasing progesterone. The same effect can be achieved by eating raw carrots (especially with coconut oil/olive oil dressing) every day, to reduce the amount of bacterial toxins absorbed, and to help in the excretion of estrogen. Finally, long hours of daylight are known to increase progesterone production, and long hours of darkness are stressful. Annually, our total hours of day and night are the same regardless of latitude, but different ways of living, levels of artificial illumination, etc., have a strong influence on our hormones. In some animal experiments, prolonged exposure to light has delayed some aspects of aging.

General aging contributes to the specific changes that lead to menopause, but the animal experiments show that fertility can be prolonged to a much greater age by preventing excitotoxic exhaustion of the hypothalamic nerves. The question that still needs to be more clearly answered is, to what extent can general aging be prevented or delayed by protecting against the excitotoxins? Minimizing estrogen (and cortisone) with optimal thyroid activity, and maximizing pregnenolone and progesterone to prevent excitotoxic cell fatigue, can be done easily. A diet low in iron and unsaturated fats protects the respiratory apparatus from the damaging effects of excessive excitation, and—since pregnenolone is formed in the mitochondrion—also helps to prevent the loss of these hormones.

Milk in Context

Allergies, Ecology, and Some Myths

Ray Peat's Newsletter, 2011

Food allergies are becoming much more common in recent decades, especially in industrialized countries. Most attention has been given to theories about changes in people, such as the reduction in infectious diseases and parasites, or vitamin D deficiency, or harmful effects from vaccinations, and little attention has been given to degradation of the food supply.

Our food cultures, like linguistic and moral cultures, give us some assumptions or theories about the way the world should be, and if these beliefs aren't questioned and tested, they can permeate the culture of science, turning the research process into a rationalization of accepted opinions.

In general, those who pay for research are those with an investment in or commitment to the preservation and expansion of the existing systems of production and distribution. Cheap mass production, durability and long shelf-life are more important than the effects of foods on health. The biggest industries are usually able to keep public attention away from the harm they do.

The historical economic importance of cereals and beans is reflected in the nutritional and biochemical research literature, which has paid relatively little attention to basic questions about human adaptation to the ecosystems. From the early petrochemical "Green Revolution" to the contemporary imposition of genetically altered seeds, the accumulated economic power of the food industry has taken control of the food culture.

In evaluating each research publication relating to nutrition and health, we should ask what alternative possibilities are being neglected, for "practical" reasons, cultural preferences, and business interests.

Some people with an ecological concern have argued that grains and beans can most economically provide the proteins and calories that people need, but good nutrition involves much more than the essential nutrients.

"Efficient" industrial agriculture has been concerned with cheaply producing those important nutrients, and their critics have focussed

on their use of toxic chemicals, on the social damage they produce, the degradation of the soil, the toxic effects of genetic modification, their unsustainable use of petroleum, and occasionally on the lower nutritional value of chemically stimulated crops.

I think far too little attention is being given to the effects of abnormal and stressful growth conditions on the plants' natural defense systems. Plants normally synthesize some toxins and inhibitors of digestive enzymes to discourage attacks by bacteria, fungi, insects, and other predators. When a plant is injured or otherwise stressed, it produces more of the defensive substances, and very often they communicate their stress to other plants, and the resulting physiological changes can cause changes in seeds that affect the resistance of the progeny.[1]

One of many substances produced by plants in response to injury is chitinase, an enzyme that breaks down chitin, a polysaccharide that is a structural component of fungi and insects. Chitinase, which is produced by bacteria and humans, as well as by plants and other organisms, is involved in developmental processes as well as in the innate immune system. In plants, the enzyme is induced by ethylene and salicylate, in animals by estrogen, light damage, and infections, and can be demonstrated in polyps and cancers.

The two main classes of plant allergens are the stress-induced chitinases, and seed storage proteins, such as gluten. The chitinase allergens are responsible for reactions to latex (which is secreted by rubber trees in reaction to a wound), bananas, avocados, many other fruits and vegetables, and some types of wood and other plant materials. Intensive agricultural methods are increasing the formation of the defensive chemicals, and the industrialized crops are responsible for the great majority of the new allergies that have appeared in the last 30 years.

The presence of the chitinase family of proteins in humans was first discovered in the inflamed asthmatic lung. It was then found at high levels in the uterine endometrium at the time of implantation of the embryo (an inflammation-like situation) and in the uterus during premature labor. Since estrogen treatment is known to increase the incidence of asthma and other inflammations, the appearance of chitinase also in the uterus in estrogen dominated conditions is interesting, especially when the role of estrogen in celiac disease (in effect an allergy to gluten) is considered. Celiac disease is more prevalent among females, and it involves the immunological cross-reaction to an antigen in the

estrogen-regulated transglutaminase enzyme and the gluten protein. The (calcium-regulated) transglutaminase enzyme is involved in the cross-linking of proteins in keratinized cells, in fibrotic processes in the liver, and in cancer. (People with celiac disease often suffer from osteoporosis and urinary stone deposition, showing a general problem with calcium regulation.)

This means that estrogen and stress cause the appearance of antigens in the human or animal tissues that are essentially the same as the stress-induced and defensive proteins in plant tissues. A crocodile might experience the same sort of allergic reaction when eating estrogen-treated women and when eating commercial bananas.

The various states of the innate immune system have been neglected by immunologists, for example in relation to organ transplantation. The "major histocompatibility" antigens are matched, but organ transplants still sometimes fail. A study found that the livers from young men had a high survival rate when transplanted into either men or women, but the livers of older women donors were rejected at a high rate when transplanted into either men or women. Exposure to estrogen increases intracellular calcium and the unsaturation of fatty acids in tissue lipids, and the expression of enzymes such as chitinase and transglutaminase, and the various enzymes in the structure-sensitive estrogen-controlled metabolic pathways.

Estrogen's actions are closely and pervasively involved with the regulation of calcium, and these changes affect the basic tissue structures and processes that constitute the innate immune system. Estrogen's effect in increasing susceptibility to "autoimmune" diseases hasn't yet been recognized by mainstream medicine.

The chemist Norman Pirie argued convincingly that leaf protein had much higher nutritional value than grain and bean proteins, and that it had the potential to be much more efficient economically, if it could be separated from the less desirable components of leaves.

The amino acid composition and nutritional value of leaf protein is similar to milk protein, which is understandable since cows produce milk from the amino acids produced in their rumens by bacteria digesting the leaves the cows have eaten. The bacteria perform the refining processes that Pirie believed could be done technologically, and they also degrade or detoxify the major toxins and allergens.

The nutrients produced in the cow's rumen are selectively absorbed into the cow's bloodstream, where the liver can further filter out any toxins before the amino acids and other nutrients are absorbed by the udder to be synthesized into milk. If cows are fed extremely bad diets, for example with a very large amount of grain, the filtering process is less perfect, and some allergens can reach the milk, but since sick cows are less profitable than healthy cows, dairies usually feed their cows fairly well.

In a recent study of 69,796 hospitalized newborns, a diagnosis of cow's milk allergy was made in 0.21 % of them. Among those whose birthweight had been less than a kilogram, 0.35 % of them were diagnosed with the milk allergy. Gastrointestinal symptoms were the main reason for the diagnosis, but a challenge test to confirm the diagnosis was used in only 15 % of the participating hospitals, and a lymphocyte stimulation test was used in only 5.5 % of them.[2] There are many publications about milk allergies, but they generally involve a small group of patients, and the tests they use are rarely evaluated on healthy control subjects.

Several surveys have found that of children who have a diagnosed milk allergy, about 2/3 of them grow out of the allergy.

People who have told me that they have had digestive problems with milk have sometimes found that a different brand of milk doesn't cause any problem.

Milk with reduced fat content is required by U.S. law to have vitamins D and A added. The vehicle used in the vitamin preparation, and the industrial contaminants in the "pure" vitamins themselves, are possible sources of allergens in commercial milk, so whole milk is the most likely to be free of allergens.

A thickening agent commonly used in milk products, carrageenan, is a powerful allergen that can cause a "pseudo-latex allergy."[3] It is a sulfated polysaccharide, structurally similar to heparin. There are good reasons to think that its toxic effects are the result of disturbance of calcium metabolism.[4,5]

Besides the idea of milk allergy, the most common reason for avoiding milk is the belief that the genes of some ethnic groups cause them to lack the enzyme, lactase, needed to digest milk sugar, lactose, and that this causes lactose intolerance, resulting in gas or diarrhea when milk is consumed. Tests have been reported in which a glass of milk

will cause the lactase deficient people to have abdominal pain. However, when intolerant people have been tested, using milk without lactose for comparison, there were no differences between those receiving milk with lactose or without it. The "intolerant" people consistently tolerate having a glass with each meal.

When a group of lactase deficient people have been given some milk every day for a few weeks, they have adapted, for example with tests showing that much less hydrogen gas was produced from lactose by intestinal bacteria after they had adapted.[6]

Bacterial overgrowth in the small intestine can be caused by hypothyroidism,[7] and the substances produced by these bacteria can damage the lining of the small intestine, causing the loss of lactase enzymes.[8]

Another hormonal condition that probably contributes to lactase deficiency is progesterone deficiency, since a synthetic progestin has been found to increase the enzyme.[9] The particular progestin they used lacks many of progesterone's effects, but it does protect against some kinds of stress, including high estrogen and cortisol. This suggests that stress, with its increased ratio of estrogen and cortisol to progesterone, might commonly cause the enzyme to decrease.

Two other ideas that sometimes cause people to avoid drinking milk and eating cheese are that they are "fattening foods," and that the high calcium content could contribute to hardening of the arteries.

When I traveled around Europe in 1968, I noticed that milk and cheese were hard to find in the Slavic countries, and that many people were fat. When I crossed from Russia into Finland, I noticed there were many stores selling a variety of cheeses, and the people were generally slender. When I lived in Mexico in the 1960s, good milk was hard to find in the cities and towns, and most women had fat hips and short legs. Twenty years later, when good milk was available in all the cites, there were many more slender women, and the young people on average had much longer legs. The changes I noticed there reminded me of the differences I had seen between Moscow and Helsinki, and I suspect that the differences in calcium intake were partly responsible for the changes of physique.

In recent years there have been studies showing that regular milk drinkers are less fat than people who don't drink it. Although the high quality protein and saturated fat undoubtedly contribute to milk's anti-obesity effect, the high calcium content is probably the main factor.

The parathyroid hormone (PTH) is an important regulator of calcium metabolism. If dietary calcium isn't sufficient, causing blood calcium to decrease, the PTH increases, and removes calcium from bones to maintain a normal amount in the blood. PTH has many other effects, contributing to inflammation, calcification of soft tissues, and decreased respiratory energy production.

When there is adequate calcium, vitamin D, and magnesium in the diet, PTH is kept to a minimum. When PTH is kept low, cells increase their formation of the uncoupling proteins, that cause mitochondria to use energy at a higher rate, and this is associated with decreased activity of the fatty acid synthase enzymes.

These changes are clearly related to the anti-obesity effect of calcium, but those enzymes are important for many other problems.

The "metabolic syndrome," that involves diabetes, hypertension, and obesity, is associated with high PTH.[10]

Alzheimer's disease involves decreased mitochondrial activity and low levels of the uncoupling proteins. There is evidence that milk drinkers are protected against dementia.[11] Cancer involves increased activity of the fatty acid synthase enzymes. Increased calcium consumption beneficially affects both sets of enzymes, uncoupling proteins and fatty acid synthase.

Multiple sclerosis relapses consistently occur at times of high PTH, and remissions consistently occur at times of low PTH.[12] PTH increases the activity of nitric oxide synthase, and nitric oxide is a factor in the vascular leakiness that is so important in MS.

There are components of milk that might protect against tooth decay by inhibiting the binding of bacteria to teeth.[13]

David McCarron has published a large amount of evidence showing how calcium deficiency contributes to high blood pressure. The chronic elevation of PTH caused by calcium deficiency causes the heart and blood vessels to retain calcium, making them unable to relax fully.

Intravenous infusion of calcium can relax blood vessels and improve heart function. The suppression of PTH is probably the main mechanism.

PTH (like estrogen) causes mast cells to release promoters of inflammation, including histamine and serotonin. Serotonin and nitric oxide contribute to increasing PTH secretion.

Removal of the parathyroid gland has reduced heart problems and mortality[14] and insomnia[15,16] in people with kidney disease and excess PTH.

Increased carbon dioxide, for example when adapted to high altitude, can greatly decrease PTH. Frequent, but smaller, meals can reduce PTH.

Cancer cells often secrete PTH and related proteins with similar effects on calcium, and the PTH stimulates the growth and invasiveness of prostate cancer[17] cells, and seems to be as closely involved with breast cancer. The PTH-related protein is associated with calcification in breast cancer.[18] Microscopic calcium crystals themselve produce inflammation.[19]

Besides being an ecologically favorable source of calcium, protein, sugar, and fat, the composition of milk causes it to be digested efficiently, supporting the growth of bacteria that are relatively safe for the intestine and liver, and reducing the absorption of endotoxin.

Dividing any food into smaller meals can lower the PTH, and milk is a convenient food to use in small amounts and frequently.

Some amino acids directly stimulate insulin secretion, decreasing blood sugar and leading to the secretion of cortisol in reaction to the depression of blood glucose. The presence of lactose in milk, and of fat, to slow absorption of the amino acids, helps to minimize the secretion of cortisol. The main protein of milk, casein, seems to have some direct antistress effects.[20]

Since milk's primary biological function is to support the growth of a young animal, some of its features make it inappropriate as a sole food for an adult. To support cell division and growth, the methionine and tryptophan content of milk is higher than would be optimal for an adult animal, and the phosphate might be slightly more than needed, in relation to the calcium. Since the fetus stores a large amount of iron during gestation, the iron content of milk is low, and when a young animal has used the stored iron, its continuing growth requires more iron than milk provides. However, for an adult, the low iron content of milk and cheese makes these foods useful for preventing the iron overload that often contributes to the degenerative diseases.

Combining milk and cheese with fruits adds to the antistress effect. The additional sugar and potassium and other minerals allow the milk protein to be used more efficiently, by moderating the secretion of cortisol, and helping to inhibit the secretion of PTH.

Substances such as PTH, nitric oxide, serotonin, cortisol, aldosterone, estrogen, thyroid stimulating hormone, and prolactin have regulatory and adaptive functions that are essential, but that ideally should act only intermittently, producing changes that are needed momentarily. When the environment is too stressful, or when nutrition isn't adequate, the organism may be unable to mobilize the opposing and complementary substances to stop their actions. In those situations, it can be therapeutic to use some of the nutrients as supplements. Calcium carbonate (eggshell or oyster shell, for example) and vitamins D and K, can sometimes produce quick antistress effects, alleviating insomnia, hypertension, edema, inflammations and allergies, etc., but the regular use of milk and cheese can prevent many chronic stress-related diseases.

Mitochondria and Mortality

Diet, Exercise, and Medicine, Damaging or Repairing Respiratory Metabolism

Ray Peat's Newsletter, 2016

Main Ideas and Context

- Lactic acid and carbon dioxide have opposing effects.
- Intense exercise damages cells in ways that cumulatively impair metabolism. There is clear evidence that glycolysis, producing lactic acid from glucose, has toxic effects, suppressing respiration and killing cells. Within five minutes, exercise lowers the activity of enzymes that oxidize glucose. Diabetes, Alzheimer's disease, and general aging involve increased lactic acid production and accumulated metabolic (mitochondrial) damage.
- The products of glycolysis, lactic acid and pyruvic acid, suppress oxidation of glucose.
- Adaptation to hypoxia or increased carbon dioxide limits the formation of lactic acid. Muscles are 50 % more efficient in the adapted state; glucose, which forms more carbon dioxide than fat does when oxidized, is metabolized more efficiently than fats, requiring less oxygen.
- Lactic acidosis, by suppressing oxidation of glucose, increases oxidation of fats, further suppressing glucose oxidation.
- Estrogen is harmful to mitochondria, progesterone is beneficial.
- Progesterone's brain-protective and restorative effects involve mitochondrial actions.
- Thyroid hormone, palmitic acid, and light activate a crucial respiratory enzyme, suppressing the formation of lactic acid. Palmitic acid occurs in coconut oil, and is formed naturally in animal tissues. Unsaturated oils have the opposite effect.
- Heart failure, shock, and other problems involving excess lactic acid can be treated "successfully" by poisoning glycolysis with dichloroacetic acid, reducing the production of lactic acid, increasing the oxidation of glucose, and increasing cellular ATP concentration. Thyroid, vitamin B_1, biotin, etc., do the same.

Some Definitions

- Glycolysis: The conversion of glucose to lactic acid, providing some usable energy, but many times less than oxidation provides.
- Lactic acid, produced by splitting glucose to pyruvic acid followed by its reduction, is associated with calcium uptake and nitric oxide production, depletes energy, contributing to cell death.
- Crabtree effect: Inhibition of cellular respiration by an excess of glucose; excess of glucose promotes calcium uptake by cells.
- Pasteur effect: Inhibition of glycolysis (fermentation) by oxygen.
- Randle effect: The inhibition of the oxidation of glucose by an excess of fatty acids. This lowers metabolic efficiency. Estrogen promotes this effect.
- Lactated Ringer's solution: A salt solution that has been used to increase blood volume in treating shock; the lactate was apparently chosen as a buffer in place of bicarbonate, as a matter of convenience rather than physiology. This solution is toxic, partly because it contains the form of lactate produced by bacteria, but our own lactate, at higher concentrations, produces the same sorts of toxic effect, damaging mitochondria.
- Estrogenic phytotoxins damage mitochondria, kill brain cells; tofu is associated with dementia.

SINCE reading Warburg's publications in the late 1960s and early 70s, and doing my own research on tissue respiration, I have been convinced that Warburg was on the right track in seeing mitochondrial respiration as the controlling influence in cell differentiation, and in seeing cancer as a reversion to a primitive form of life based on a "respiratory defect." Harry Rubin's studies of cells in culture have expanded Warburg's picture of the process of cancerization, showing that genetic changes occur only after the cells have been transformed into cancer.

It is now well recognized that defective mitochondrial respiration is a central factor in diseases of muscles, brain, liver, kidneys, and other organs. The common view has been that the mitochondrial defects are produced by genetic defects, that are either inherited or acquired, and are irreversible.

Mitochondria depend on some genes in the nuclear chromosomes, but they also contain some genes, and mutations in these specific mitochondrial genes have been associated with various diseases, and with aging. Although these aren't the genes that the cancer establishment has focussed on as "the cause" of cancer, for people interested in the achievements of Warburg and Rubin, it is important to know whether mutations in these mitochondrial genes are the cause of respiratory defects, or whether a respiratory defect causes the mutations. Recent research seems to show that physiological problems precede and cause the mutations.

Warburg believed that mitochondria supported specialized cell functions by concentrating themselves in the places where energy is needed. This idea has some interesting implications. For example, when the amount of thyroid hormone is increased, or when the organism adapts to a high altitude, the number of mitochondria increases. But in energy deficient states such as diabetes, they don't. How are these crucial organelles called into existence by the hormone that increases respiration and energy, and also by the hypoxic conditions of high altitudes? In both of these conditions, the availability of oxygen is limiting the ability to produce energy. In both conditions, carbon dioxide concentration in tissue is higher, in one case, because thyroid stimulates its production, in the other, because the Haldane effect limits its loss from the lungs.

Could carbon dioxide, a major product of mitochondria, help to call mitochondria into existence? My answer to this is "yes," and it will help to briefly explain how I see mitochondria. Although I have no hesitancy

in accepting that organelles can be exchanged between species, and that it is conceivable that mitochondria might have been derived from symbiotic bacteria, I am reluctant to believe that something happens just because it could happen. For example, Francis Crick proposed that life on earth originated when genes arrived here on space dust from some other world. That's a theoretical possibility, but what's the point? It just avoids explaining how the highly organized material came into existence somewhere else, and it probably seriously interfered with the consideration of the ways life could arise here. Similarly, some people like to think that mitochondria and chloroplasts were originally bacteria, that came into symbiosis with another kind of living material, consisting of nucleus and cytoplasm. Like Crick's "space germs," it can be argued that it's possible, but the problem is that this explanation can stop people from thinking freshly about the nature of the various organelles, and how they came to exist. (How did cells originate? How did mitochondria originate? "Germs.")

Since I have a view of how cells came to exist, under conditions that exist on earth, I should consider whether that view doesn't also reasonably account for their various components. Sidney Fox's proteinoid microspheres provide a good model for the spontaneous formation of primitive cells; variations of that idea can account for the formation of organelles (such as mitochondria and nuclei within cells, and chromosomes within nuclei). The value of this idea, of a self-stimulating process in mitochondrial generation, is that it suggests many ways to test the idea experimentally, and it suggests explanations for developmental and pathological processes that otherwise would have no coherent explanation.

Proteinoid microspheres and coacervates form by acquiring molecules from solution, condensing them into a separate phase, with its own physical properties. At every phase boundary, there are numerous physical forces, especially electronic properties, that make each kind of interface different from other kinds. Small changes of pH, temperature, of salts and other solutes can alter the interfacial forces, causing particles to dissolve, or grow, or fragment, or to move. In the way that carbon dioxide alters the shapes and electrical affinities of hemoglobin and other proteins, I propose that it increases the stability of the mitochondrial coacervate, causing it to "recruit" additional

proteins from its external environment, as well as from its own synthetic machinery, to enlarge both its structure and its functions.

In the relative absence of carbon dioxide, or excess of alternative solutes and adsorbents, such as lactic acid, the stability of the mitochondrial phase would be decreased, and the mitochondria would be degraded in both structure and function. As the back side of the idea that carbon dioxide stabilizes and activates mitochondria, the idea that lactic acid is involved in the degrading of mitochondria can also be tested experimentally, and it is already supported by a considerable amount of circumstantial evidence.

This combination of sensitivity to the environment, with a kind of positive feedback or inertia either upward or downward, corresponds to what we actually see in mitochondrial physiology and pathology.

The Crabtree effect, which is the suppression of respiration by glycolysis, is often described as the simple opposite of the Pasteur effect, in which respiration limits glycolysis to the rate that allows its product to be consumed oxidatively. But the Pasteur effect is a normal sort of control system; when the Pasteur effect fails, as in cancer, there is glycolysis which is relatively independent of respiration, causing sugar to be consumed inefficiently. Embryonic tissues sometimes behave in this manner, leading to the suggestion that glycolysis is closely related to growth. Unlike the logical Pasteur effect, the Crabtree effect tends to lower cellular energy and adaptability. Looking at many situations in which increasing the glucose supply increases lactic acid production and suppresses respiration, leading to maladaptive decrease in cellular energy, I have begun thinking of lactic acid as a toxin. The use of Ringer's lactate solution in medicine has led many people to assume that lactate must be beneficial, or they wouldn't put it in the salt solution that is often used in emergencies; however, I think its use here, as a buffer, is simply a convenience, because of the instability of some bicarbonate solutions.

On the organismic level, it is clear that lactic acid is "the essence of hyperventilation," and that it produces edema and malfunction on a grand scale: The panic reaction, shock lung, vascular leakiness, brain swelling, and finally multiple organ failure, all can be traced to an excess of lactic acid, and the related features of hyperventilated physiology.

Otto Warburg apparently thought of lactate as simply a sign of the respiratory defect that characterizes cancer. V. S. Shapot at least hinted

at its possible role in turning on the catabolic reactions leading to cancer cachexia (wasting). I think a good case can be made for lactate as the cause of the respiratory defect in cancer, just as it is usually the immediate cause of the respiratory derangement of hyperventilation on the organismic level.

The Crabtree effect is usually thought of as just something that happens in tumors, and some tissues that are very active glycolytically, and some bacteria, when they are given large amounts of glucose. But when we consider lactate, which is produced by normal tissues when they are deprived of oxygen or are disturbed by a stress reaction, the Crabtree effect becomes a very general thing. The "respiratory defect" that we can see on the organismic level during hyperventilation, is very similar to the "systemic Crabtree effect" that happens during stress, in which respiration is shut down while glycolysis is activated. Since oxidative metabolism is many times more efficient for producing energy than glycolysis is, it is maladaptive to shut it down during stress.

Since the presence of lactate is so commonly considered to be a normal and adaptive response to stress, the shut-down of respiration in the presence of lactate is generally considered to be caused by something else, with lactate being seen as an effect rather than a cause. Nitric oxide and calcium excess have been identified as the main endogenous antirespiratory factors in stress, though free unsaturated fatty acids are clearly involved, too. However, glycolysis, and the products of glycolysis, lactate and pyruvate, have been found to have a causal role in the suppression of respiration; it is both a cause and a consequence of the respiratory shutdown, though nitric oxide, calcium, and fatty acids are closely involved,

Since lactic acid is produced by the breakdown of glucose, a high level of lactate in the blood means that a large amount of sugar is being consumed; in response, the body mobilizes free fatty acids as an additional source of energy. An increase of free fatty acids suppresses the oxidation of glucose. (This is called the Randle effect, glucose-fatty acid cycle, substrate-competition cycle, etc.) Women, with higher estrogen and growth hormone, usually have more free fatty acids than men, and during exercise oxidize a higher proportion of fatty acids than men do. This fatty acid exposure "decreases glucose tolerance," and undoubtedly explains women's higher incidence of diabetes. While most fatty acids inhibit the oxidation of glucose without immediately inhibiting glycol-

ysis, palmitic acid is unusual, in its inhibition of glycolysis and lactate production without inhibitng oxidation. I assume that this largely has to do with its important function in cardiolipin and cytochrome oxidase.

Exercise, like aging, obesity, and diabetes, increases the levels of circulating free fatty acids and lactate. But ordinary activity of an integral sort, activates the systems in an organized way, increasing carbon dioxide and circulation and efficiency. Different types of exercise have been identified as destructive or reparative to the mitochondria; "concentric" muscular work is said to be restorative to the mitochondria. As I understand it, this means contraction with a load, and relaxation without a load. The heart's contraction follows this principle, and this could explain the observation that heart mitochondria don't change in the course of ordinary aging.

When a person has an accident, or surgery, and goes into shock, the degree of lactic acidema is recognized as an indicator of the severity of the problem. Lactated Ringer's solution has been commonly used to treat these people, to restore their blood pressure. But when prompt treatment with lactated Ringer's solution has been compared with no early treatment at all, the patients who are not "resuscitated" do better than those who got the early treatment. And when Ringer's lactate has been compared with various other solutions, synthetic starch solutions, synthetic hemoglobin polymer solution, or simply a concentrated solution of sodium chloride, those who received the lactate solution did least well. For example, of 8 animals treated with another solution, 8 survived, while among 8 treated with Ringer's lactate, 6 died.

Mitochondrial metabolism is now being seen as the basic problem in aging and several degenerative diseases. The tendency has been to see random genetic deterioration as the driving force behind mitochondrial aging. Genetic repair in mitochondria was assumed not to occur. However, recently two kinds of genetic repair have been demonstrated. One in which the DNA strand is repaired, and another, in which sound mitochondria are "recruited" to replace the defective, mutated, "old" mitochondria.

In ordinary nuclear chromosomal genes, DNA repair is well known. The other kind of repair, in which unmutated cells replace the. genetically damaged cells, has been commonly observed in the skin of the face: During intense sun exposure, mutant cells accumulate; but after a

period in which the skin hasn't been exposed to the damaging radiation, the skin is made up of healthy "young" cells.

In the way that the skin can be seen to recover from genetic damage, that had been considered to be permanent and cumulative, simply by avoiding the damaging factor, mitochondrial aging is coming to be seen as both avoidable and repairable.

The stressful conditions that physiologically harm mitochondria are now being seen as the probable cause for the mitochondrial genetic defects that accumulate with aging. Stressful exercise, which has been known to cause breakage of the nuclear chromosomes, is now seen to damage mitochondrial genes, too. Providing energy, while reducing stress, seems to be all it takes to reverse the accumulated mitochondrial genetic damage.

Fewer mitochondrial problems will be considered to be inherited, as we develop an integral view of the ways in which mitochondrial physiology is disrupted. Palmitic acid, which is a major component of the cardiolipin which regulates the main respiratory enzyme, becomes displaced by polyunsaturated fats as aging progresses. Copper tends to be lost from this same enzyme system, and the state of the water is altered as the energetic processes change.

While the flow of carbon dioxide moves from the mitochondrion to the cytoplasm and beyond, tending to remove calcium from the mitochondrion and cell, the flow of lactate and other organic ions into the mitochondrion can produce calcium accumulation in the mitochondrion, during conditions in which carbon dioxide synthesis, and consequently urea synthesis, are depressed, and other synthetic processes are changed.

Glycolysis produces both pyruvate and lactate, and excessive pyruvate produces almost the same inhibitory effect as lactate; since the Crabtree effect involves nitric oxide and fatty acids as well as calcium, I think it is reasonable to look for the simplest sort of explanation, instead of trying to experimentally trace all the possible interactions of these substances; a simple physical competition between the products of glycolysis and carbon dioxide, for the binding sites, such as lysine, that would amount to a phase change in the mitochondrion. Glucose, and apparently glycolysis, are required for the production of nitric oxide, as for the accumulation of calcium, at least in some types of cell, and these coordinated changes, which lower energy production, could be produced by a reduction in carbon dioxide, in a physical change even

more basic than the energy level represented by ATP. The use of Krebs cycle substances in the synthesis of amino acids, and other products, would decrease the formation of CO_2, creating a situation in which the system would have two possible states, one, the glycolytic stress state, and the other, the carbon dioxide producing energy-efficient state.

Besides the frequently discussed interactions of excessively accumulated iron with the unsaturated fatty acids, producing lipid peroxides and other toxins, the accumulated calcium very probably forms some insoluble soaps with the free fatty acids which are released even from intracellular fats during stress. The growth of new mitochondria probably occasionally leaves behind such useless materials, combining soaps, iron, and porphyrins remaining from damaged respiratory enzymes.

When the background of carbon dioxide is high, circulation and oxygenation tend to prevent the anaerobic glycolysis that produces toxic lactic acid, so that a given level of activity will be harmful or helpful, depending on the level of carbon dioxide being produced at rest.

Preventively, avoiding foods containing lactic acid, such as yogurt and sauerkraut, would be helpful, since bacterial lactic acid is much more toxic than the type that we form under stress. Avoiding the stress-promoting antithyroid unsaturated oils is extremely important. Their role in diabetes, cancer, and other age-related and degenerative diseases (and I think this includes the estrogen-promoted autoimmune diseases) is well established. Avoiding phytoestrogens and other things that increase estrogen exposure, such as protein deficiency, is important, because estrogen causes increased levels of free fatty acids, increases the tendency to metabolize them at the expense of glucose metabolism, increases the tissue content of unsaturated fatty acids, and inhibits thyroid functions.

Light promotes glucose oxidation, and is known to activate the key respiratory enzyme. Winter sickness (including lethargy and weight gain), and night stress, have to be included within the idea of the "respiratory defect," shifting to the antirespiratory production of lactic acid, and damaging the mitochondria.

Therapeutically, even powerful toxins that block the glycolytic enzymes can improve functions in a variety of organic disturbances "associated with" (caused by) excessive production of lactic acid. Unfortunately, the toxin that has become standard treatment for lactic acidosis—dichloroacetic acid—is a carcinogen, and eventually produces liver dam-

age and acidosis. But several nontoxic therapies can do the same things: Palmitate (formed from sugar under the influence of thyroid hormone, and found in coconut oil), vitamin Bl, biotin, lipoic acid, carbon dioxide, thyroid, naloxone, acetazolamide, for example. Progesterone, by blocking estrogen's disruptive effects on the mitochondria, ranks along with thyroid and a diet free of polyunsaturate fats, for importance in mitochondrial maintenance.

Multiple Sclerosis, Protein, Fats, and Progesterone

Ray Peat's Newsletter, 2009

- We are always subjected to antigenic burdens. The important question has to do with our ability to limit the inflammatory response to these burdens.
- In MS, it is clear that the inflammatory process itself is destructive, and that estrogen is a major predisposing factor. Unsaturated fatty acids, and dietary imbalance of amino acids interact closely with hyperestrogenism and hypothyroidism to produce the autoimmune degenerative diseases.
- Reduction of the mediators of inflammation is better than augmenting a single antiinflammatory agent such as cortisol. Although immunosuppressive drugs, including the "essential fatty acids," do alleviate inflammatory symptoms temporarily, they probably contribute to the underlying pathology.
- People with MS have chronically increased production of cortisol. This creates a distortion of protein assimilation, resembling a nutritional protein deficiency. Excessive serotonin and estrogen cause a relatively uncontrolled production of cortisol. A vicious circle of inflammatory mediators and amino acid imbalance can result.
- Depression, lupus, migraine, menopause, diabetes, and aging have several important metabolic features in common with MS.
- Popular therapies are illogical, and are likely to cause disease progression.
- High quality protein, thyroid, pregnenolone and progesterone tend to correct the underlying pathology. These are antiinflammatory, but they are not immunosuppressive or catabolic.
- High altitude and sunny climate are associated with a low incidence of MS.

MULTIPLE sclerosis (MS), like other autoimmune diseases, affects women more often than men (about 2 to 1), has its onset during the reproductive years (especially after the age of 30, when estrogen is very high), is often exacerbated premenstrually, and is sometimes alleviated by pregnancy,[1] when progesterone is very high. Women with

a high ratio of estrogen to progesterone have been found to have the most active brain lesions.[2] Most of the mediators of inflammation that are involved in MS—mast cells, nitric oxide (NO), serotonin, prolactin, lipid peroxidation, free fatty acids, prostaglandins and isoprostanes, and the various cytokines (IL, TNF)—are closely associated with estrogen's actions, and in animals, autoimmune diseases can be brought on by treatment with estrogen (Ahmed and Talal).

The strong association of MS with estrogen has led to an illogical, but popular and well-publicized medical conclusion that estrogen is protective against MS, and some have claimed that estrogen has beneficial therapeutic effects. This strange way of thinking has its equivalent in the idea that, since women are much more likely than men to develop Alzheimer's disease, estrogen is protective against it; or that, since women have more fragile bones than men do, and their progressive bone loss occurs during the times of their greatest exposure to estrogen, estrogen prevents osteoporosis.

In this medical environment, close associations between estrogen and degenerative diseases are acknowledged, but they are given a meaning contrary to common sense by saying that the association occurs because there isn't enough estrogen. The stove burns you because it isn't hot enough.

As Dave Barry would say, I'm not making this up. Recently well publicized articles have suggested that estrogen protects the brain (even against stroke!) because it increases serotonin and NO. There is something almost esthetically pleasing when so many major errors are concentrated into a single article. Nitric oxide and serotonin are both neurotoxic,[3–7] as a result of suppressing mitochondrial respiration. NO plays a major role in lipid peroxidation and demyelination. It's interesting to see serotonin and NO openly associated with estrogen, whose mitochondrial toxicity has been carefully hidden from public view.

There are several theories about the cause of MS, old theories about genes and viruses, and newer theories about bacteria, vitamin deficiencies, oil deficiencies, poisons, and reactions to vaccinations (especially for hepatitis B and influenza). The only theory that has been abandoned is the 19th century psychiatric theory about "hysterical paralysis," though occasionally someone does still talk about emotional causes of multiple sclerosis; the term "female hysteria" has evolved into "conversion disorder."

Each of the main theories has a few facts that seem to support it, but neglects to account for many other facts. Everyone agrees that the immune system is involved in MS in some way, but that's really where the problem starts, because of the idea that inflammation is an intrinsic part of immunity. If "inflammation is necessary and good," then it becomes a problem to define exactly where the boundary is between an appropriate reaction and a degenerative process. Edema, reduced cellular respiration, loss of normal functions, fibrosis in its various degrees, each component of inflammation can be seen in a good light, as part of a "defensive immune reaction." When tissue injury leads to repair, it "must" be seen as beneficial, even if it leads to the formation of a scar in place of functional tissue, because the comparison is between an imagined worst possible outcome, and an imperfect recovery, rather than comparing the inflammatory process with the possibility that a potentially noxious agent might have done no harm at all.

The simplest illustration of how inflammation relates to the organism's resources was an experiment in which blood glucose was varied, while an animal was exposed to chemicals that varied from mildly irritating to potentially deadly. When the animal had very low blood sugar, the mildest irritant could be deadly, but when its blood glucose was kept very high, even the deadly antigens were only mildly irritating. Varying the blood sodium concentration had similar, but weaker, effects.

There is a tendency to see inflammation not only as a normal part of immunity, but to see it as being proportional to the nature of the antigen, except when the immune system has been primed for it by previous contact, in which case the organism will either not react at all (because it has become immune), or it will react much more violently than it did on the first exposure, because it has become allergic. But, in reality, the mere concentration of glucose and sodium in the blood (and of thyroid, and many other substances that aren't considered to be part of the immune system) can make a tremendous difference in the degree of "immunological" reaction.

In the excessively sensitive condition produced by hypoglycemia, several things happen that contribute to the maladaptive exaggerated inflammatory response.

Adrenaline increases in hypoglycemia, and, if the adrenaline fails to convert glycogen into glucose, it will provide an alternative fuel by liberating free fatty acids from fat cells.

If the liberated fatty acids are unsaturated, they will cause serotonin to be secreted, and both serotonin and the unsaturated fatty acids will suppress mitochondrial respiration, exacerbating the hypoglycemia. They will stimulate the release of cytokines, activating a variety of immunological and inflammatory processes, and they will cause blood vessels to become leaky, creating edema and starting the first stages of fibrosis. Both adrenaline and serotonin will stimulate the release of cortisol, which mobilizes amino acids from tissues such as the large skeletal muscles. Those muscles contain a large amount of cysteine and tryptophan, which, among other effects, suppress the thyroid. The increased tryptophan, especially in the presence of free fatty acids, is likely to be converted into additional serotonin, since fatty acids release tryptophan from albumin, increasing its entry into the brain. Free fatty acids and increased serotonin reduce metabolic efficiency (leading to insulin resistance, for example) and promote an inflammatory state.

Fats in the blood-stream have easy access to the brain, and the unsaturated free fatty acids produce brain edema.[8,9] When brain edema is caused by vascular leakage, proteins that are normally excluded can enter. The stimulated, excited and fatigued brain exchanges glutamine for tryptophan, accelerating its uptake from the blood.

When a tissue is injured or stressed, antibodies are formed in response to the altered components of that tissue. Therefore, we could call a bruise or a sprain an autoimmune condition, but there are no commercial tests for bruised-shin antibodies. The availability of tests for specific antibodies seems to be the essential factor in classifying a condition as autoimmune, as in "autoimmune thyroiditis." Unfortunately, this way of using language is nested in a culture that is full of unrealistic ideas of causality, and thousands of people build their careers on the search for the "mutated genes that are responsible for the disease," and for the drugs that will correct the defect.

Early in the study of immunology, the focus was on antibodies. Even earlier, inflammation had been conceptualized in terms of the "humors," and other prescientific ideas. As soon as multiple sclerosis/hysterical paralysis was classified as an autoimmune disease, primitive ideas about the nature of the immune system, interacting with primitive ideas about the nature of the brain and the structure of cells, blended into the various theories of what the disease is.

Rather than seeing immunological nerve damage as the cause of all the other features of multiple sclerosis, I think it's important to look at some of the general features of the condition, as contexts in which to interpret the events in the nerves.

It has been known for a long time that the incidence of MS tends to increase with distance from the equator. Incidence is low in sunny dry climates, and at high altitudes. Two clear dietary influences have been found: eating pork, and horsemeat.

People with MS don't regulate their body temperature very well. Their nerve conduction is slow, and in normal people, conduction is faster at higher temperatures, but in people with MS the conduction is slower at the normal temperature of 98.6 °F than at lower temperatures. A subnormal temperature is also associated with old age, and with the hot flashes of menopause.

Brain metabolism of glucose is very low in multiple sclerosis, and in my own observations, the general metabolic rate is subnormal. However, some people reason that the hypometabolism is caused by the lesions, rather than vice versa.

Animals that lack the unsaturated fatty acids have a higher metabolic rate and ability to use glucose, converting it to CO_2 more readily, have a greater resistance to toxins,[10] including endotoxin[11]—preventing excessive vascular leakage—and to immunological damage,[12] and to trauma, and their neuromuscular response is accelerated while fast twitch muscles are less easily fatigued.[13]

In people with MS, the blood is more viscous, and the platelets tend to clump together more easily. Their cortisol level is higher than normal, and their pituitary adrenal-cortex-stimulating hormone is harder to suppress. This is a condition that is also seen in depression and old age. Despite the chronically elevated cortisol, people with MS typically have hypoglycemia. They are occasionally found to have low blood sodium, hyponatremia, but this is hard to determine when the blood's water content is variable. Their prolactin is likely to be high, and this can result from high estrogen, high serotonin, low sodium, or low thyroid. Drinking too much water can increase prolactin, and can damage the nerves' myelin enclosures; too much serotonin tends to cause excessive drinking. Disturbances of blood glucose, sodium, and water content can disrupt the brain's myelin structure. High estrogen disturbs the blood osmotically, making it retain too much water in relation to the solutes, and

this relates to many of estrogen's effects; since simple osmotic variations can damage the myelin structures, it seems that this mechanism should be investigated thoroughly before it is assumed that the immunological events are primary.

Mast cells, which promote inflammation by releasing substances such as histamine and serotonin (and make blood vessels leaky), are more numerous in the brain in multiple sclerosis than in normal brains. Since platelet clumping releases serotonin, and also because serotonin excess is suggested by so many other features of MS, serotonin antagonists (ondansetron and ketanserin, for example) have been used therapeutically with success.

Estrogen causes mast cells to release their inflammatory mediators, and it causes platelets to aggregate, releasing their serotonin. Since estrogen dominance is closely associated with the presence of active brain lesions, antiestrogen therapy would seem obvious in MS. Progesterone counteracts estrogen's effects on both mast cells and platelets.

Aspirin protects against a variety of inflammatory processes, but it's most famous for the inhibition of prostaglandins. While aspirin is often used to relieve pain in MS, and another inhibitor of prostaglandin synthesis, indomethacin, has been used therapeutically in MS, it would seem appropriate to investigate more carefully aspirin's possible role in preventing or relieving MS.

A simple protein deficiency has many surprising effects. It lowers body temperature, and suppresses the thyroid, but it increases inflammation and the tendency of blood to clot. Since the brain and heart and lungs require a continuous supply of essential amino acids if they are to continue functioning, in the absence of dietary protein, cortisol must be produced continuously to mobilize amino acids from the expendable tissues, which are mainly the skeletal muscles. These muscles have a high concentration of tryptophan and cysteine, which suppress the thyroid. Cysteine is excitoxic, and tryptophan is the precursor for serotonin. Presumably, their presence in, and stress-induced release from, the muscles is one of the mechanisms that reduce metabolic activity during certain types of stress.

When pregnant animals are deprived of protein, the newborn animals have abnormally high levels of serotonin, and the enzymes responsible for that excess tend to maintain the serotonin excess even when they are grown and have adequate protein. This is analogous to

the effect of excess estrogen early in life, which creates a tendency to develop breast or prostate cancer in adulthood. It would be interesting to study the gestational experience, e.g., length of gestation and birth weight, of the people who later develop MS.

Although people in the northern countries aren't normally protein-starved, they do tend to get a large part of their protein from the muscle meats. In traditional cultures, all parts of the food animals were eaten—chicken feet, heads, and necks, animals' ears and eyeballs, etc.—and so the amino acid balance was favorable for maintaining a high metabolic rate and preventing stress.

The observation that multiple sclerosis is associated with the consumption of pork and horsemeat, but not beef, lamb, or goat, is very interesting, since the fat of those animals is essentially like the fats of the plant materials that they eat, meaning that it is extremely high in linoleic and linolenic acids. The rumen of cows, sheep, and goats contains bacteria that convert the polyunsaturated fats into more saturated fats. Unsaturated fats inhibit the enzymes that digest protein, and MS patients have been reported to have poor digestion of meat.[14]

The polyunsaturated fats are in themselves toxic to mitochondria, and suppress glucose oxidation, and inhibit the thyroid function, with the same suppressive effect on the ability to oxidize glucose, but they are also turned, enzymically, into the prostaglandins, and non-enzymically, by spontaneous lipid peroxidation, into the toxic isoprostanes. The isoprostanes, and some of the prostaglandins, are elevated in the brain and other tissues of people with MS.

Lipid peroxidation is very high in multiple sclerosis. Nitric oxide (whose synthesis is promoted by estrogen in most parts of the brain) is a free radical that activates peroxidation.

Lipid peroxidation selectively destroys, naturally, the unstable polyunsaturated fats. In atherosclerosis, the blood vessel plaques contain very little unsaturated fat. This is because they are peroxidized so rapidly, but their high ratio of saturated to unsaturated fats has been used to argue that the polyunsaturated oils are "heart protective." Similar arguments are often made in MS, though some studies don't support the idea that there is a lack of any of the unsaturated fats. Since lipid peroxidation is very high, it would be reasonable to assume that there was an abundance of polyunsaturated fats being peroxidized through reactions with catalysts such as iron[15] and nitric oxide and peroxynitrile.

I believe that an important aspect of the intolerance for heat so often reported in people with MS could be the tendency of relative hyperthermia to release increased amounts of free fatty acids into the blood stream. Women, because of estrogen's effects, usually have much higher levels of free fatty acids in the blood than men do. Estrogen increases the release of free fatty acids from stored fat, and the unsaturated fats synergize with both estrogen and prolactin, increasing their effects.

Temperature regulation apparently involves some nerve cells that sense temperature very accurately, and change their activity accordingly. Water has a remarkably high heat capacity, meaning that it takes a relatively large amount of heat to change its temperature. The "disappearing heat" is being consumed by structural changes in the water. Proteins have the same sort of structural complexity as water, and together they can make effective temperature transducers, "thermometers." (Other substances tend to undergo major structural changes only as they melt or vaporize. The famous "liquid crystals" have a few distinct structural phases, but cytoplasm is like a very subtle liquid crystal.) The "thermostat cells" are actually responding to a degree of internal structure, not to the temperature in the abstract. So things that change their internal structure will modify their temperature "set-point."

Increased estrogen causes an animal to lower its temperature, and it probably does this by increasing the "structural temperature" of the thermostat cells, "melting" their internal structure. Progesterone causes the animal to increase its temperature, and it apparently does this by increasing the structure/decreasing the structural temperature of the thermostat cells. If you put ice in the thermostat, the room gets hot.

A cell's internal structure is equivalent to its readiness to work. Fatigue represents a slightly "melted" state of the cell, in which structure appears to have been consumed along with the chemical energy reserves. Experiments that demonstrated this effect were very clear, but they were ignored because they didn't fit people's stereotyped idea of the cell. With a very sensitive thermometer, it's possible to measure the heat produced by a nerve when it is stimulated. That's not surprising. But it's surprising that, when the nerve is recovering from the stimulation, it absorbs heat from its environment, lowering the temperature locally. That even violated some people's conception of "entropy," but it can easily be demonstrated that changing the form of some materials changes their

heat capacity, as when a rubber band is stretched (it gets hot), or contracts (it gets cooler).

The excitants, estrogen and cortisol, slow the conduction of nerves, because they cause its internal structure to be dissipated. They create a "pre-fatigued" state in the cell.

In experiments with rabbit hearts, Szent-Györgyi showed that estrogen decreased the heart's readiness to work, and that progesterone increased its readiness to work, and he said it did this by "building structure." He pointed out that, for a given drug or other stimulus, cells have a characteristic response, becoming either more activated or more inhibited, but he showed that, outside the normal concentration or intensity range of the stimulus, a cell's response is often reversed.

If this is the situation in the nerves in MS, it explains the strange behavior, in which warming the nerve reduces its function. The implication is that internal structure (and energy) must be restored to the nerves. In experiments that I have described in previous newsletters, increasing sodium, ATP, carbon dioxide, and progesterone, and increasing the ratio of magnesium to calcium, have been found to increase cellular energy and structure. The thyroid hormone is ultimately responsible for maintaining cells' energy and structure, and responsiveness, but if it is increased suddenly without allowing all the other factors to adjust, it will raise the temperature too suddenly. It needn't take a long time, but all the factors have to be present at the same time.

Serotonin, melatonin, estrogen, and polyunsaturated fats all tend to lower body temperature. Since estrogen and the unsaturated fats are cellular excitants, the actual decrease in body temperature helps to offset their excitatory effects.

Both bright light and high altitude tend to reduce serotonin's effects. The tissue carbon dioxide retained at high altitude reduces the incidence of many diseases, and multiple sclerosis might be affected as heart disease and cancer are. It is known that carbon dioxide is involved in myelin's regulation of its own water content. Hyperventilation, by causing a loss of carbon dioxide, releases both histamine and serotonin, making blood more viscous, while making blood vessels more permeable, and causing them to constrict.

If people with MS have developed it through the interactions of excessive estrogen, serotonin, unsaturated fats, iron, and water, and deficient thyroid, and deficient pregnenolone produced in the myelin-

forming cells (oligodendrocytes), there are many things that can be done to stop its progress, and possibly to reverse it.

Since a sudden increase in temperature will release increased amounts of the pro-inflammatory fats, things should be changed gradually. Increased salt is thermogenic, but increased magnesium is protective against hyperthermia, so increased magnesium (epsom salts baths, for example, coffee, fruits, some vegetables and meats) would be helpful. Magnesium is rapidly lost from cells in hypothyroidism. Sugar, when accompanied by fats and minerals, as in milk, is needed to lower cortisol, and to maintain thyroid activity. Balanced proteins, such as cheese, potatoes, eggs, and beef- or lamb-broth (for the gelatin and mineral content in particular) will prevent the tryptophan excess that suppresses the thyroid and is potentially a nerve toxin. Saturated fats, used regularly, reduce the immediate toxic antimetabolic effects of the stored unsaturated fats, but it takes a long time to change the balance of stored fats.

Since aspirin lowers temperature, is antiinflammatory, in some situations antiestrogenic, and is a powerful antioxidant, it is likely that it would alleviate symptoms and prevent progression of MS, as it does in other degenerative diseases. Since platelet aggregation is likely to be involved in the focuses of inflammation, aspirin might help to prevent the formation of new areas of damage.

While the glucocorticoids are useful for their antiinflammatory actions, cortisol is known to promote the killing of brain cells by excitotoxicity. Since estrogen decreases GABA, and both estrogen and serotonin activate the excitatory amino acid transmitters, the addition of synthetic glucocorticoids to the pre-existing cortisol excess is likely to damage parts of the brain in addition to the inflamed areas.

The excess cortisol of depression, old age, and hyperestrogenism often comes down with use of a thyroid supplement, but pregnenolone has a very direct action (in opposition to serotonin) that can quiet the pituitary, reducing ACTH and cortisol. Progesterone has some similar effects, and is protective against excess cortisol, and is a major factor in nerve and brain restoration. Thyroid, progesterone, and pregnenolone are all involved in the formation of new myelin, and in the prevention of the edema that damages it.

Since thyroid and progesterone decrease the formation of estrogen in inflamed tissue, while cortisol stimulates its formation, it would

seem wise to use thyroid and progesterone for their immediate anti-inflammatory effects, which include the inhibition of NO formation,[1] and their lack of the excitotoxic, estrogen-stimulating effects of the glucocorticoids. While the glucocorticoids are catabolic and liberate cysteine and tryptophan from muscles, thyroid and progesterone are not catabolic, and protect against the toxic consequences of those amino acids.

Multiple Sclerosis and Other Hormone-Related Brain Syndromes

Ray Peat's Newsletter, 2013

SINCE I am trying to discuss a complex matter in a single article, I have separately outlined the essential technical points of the argument in a section at the beginning, then I explain how my ideas on the subject developed, and finally there is a glossary. If you start with "Short-day brain stress," "Estrogen's effects," and "Symptoms and therapies," you will have the general picture, and can use the other sections to fill in the technical details.

The Argument

1) The hormones pregnenolone, thyroid, and estrogen are involved in several ways with the changes that occur in multiple sclerosis, but no one talks about them.

2) The process of myelination is known to depend on the thyroid hormone. The myelinating cells are the oligodendroglia (oligodendrocytes) which appear to stop functioning in MS (and sometimes to a milder degree in Alzheimer's disease, and other conditions). The cells' absorption of thyroid hormone is influenced by dietary factors.

3) The oligodendrocytes are steroid-producing cells,[1] and steroidogenesis is dependent on thyroid hormone, and on thyroid-dependent respiratory enzymes and on the heme-enzyme P-450scc, which are all sensitive[2] to poisoning by carbon monoxide and cyanide. The steroid produced by the oligodendrocytes is pregnenolone, which is known to have a profound anti-stress action,[3] and which appears to be the main brain-protective steroid.

4) Lesions resembling those of MS can be produced experimentally by carbon monoxide or cyanide poisoning.[4] The lesions tend to be associated with individual small blood vessels, which are likely to contain clots. (Since all animals have enzymes to detoxify cyanide, this poison is apparently a universal problem, and can originate in the bowel. "Detoxified" cyanide is still toxic to the thyroid.)

5) Pregnenolone and progesterone protect against nerve damage[5] by the excitotoxic amino acids (glutamic acid, aspartic acid, monosodium glutamate, aspartame, etc.), while estrogen[6,7] and cortisol[8,9] are nerve-destroying, acting through the excitotoxic amino acids. Excitotoxins destroy certain types of nerve, especially the dopaminergic and cholinergic types, leaving the noradrenergic types,[10] paralleling the changes that occur in aging. The clustering of oligodendrocytes around deteriorating nerve cells could represent an adaptive attempt to provide pregnenolone to injured nerve cells.

6) The involvement of hormones and environmental factors probably accounts for the intermittent progress of multiple sclerosis. To the extent that the environmental factors can be corrected, the disease can probably be controlled.

Short-Day Brain Stress

Shortly after I moved from Mexico to Montana, one of my students, a 32-year-old woman, began having the same sensory symptoms her older sister had experienced at the same age, at the onset of multiple sclerosis. Vertigo and visual distortions of some sort made her consider withdrawing from the university. I'm not sure why she tried eating a whole can of tuna for lunch a couple of days after the onset of symptoms, but it seemed to alleviate the symptoms, and she stayed on a high protein diet and never had a recurrence. She told me some of the lore of MS: That it mostly affects young adults between the ages of 20 and 40, that it is common in high latitudes and essentially unknown in the tropics, and that it is sometimes exacerbated by pregnancy and stress. (Later, I learned that systemic lupus erythematosis and other "auto-immune" diseases also tend to occur mainly during the reproductive years. I discussed some of the implications of this in "Bean Syndrome.")

Having enjoyed the mild climate of Mexico, I became very conscious of the harm done to us by northern winters, and began developing the idea of "winter sickness." In 1966-67, allergies, PMS, weight gain, colitis, and arthritis came to my attention as winter-related problems, and I assumed that the high-latitude incidence of MS related to what I was seeing and experiencing. Studies in Leningrad began revealing

that mitochondria are injured during darkness, and repaired during daylight. I observed that hamsters' thymus glands shrank in the winter and regenerated in the summer; shrinkage of the thymus gland is a classical feature of stress, and usually reflects the dominance of cortisone, though estrogen and testosterone also cause it to shrink. Winter's darkness is stressful in a very fundamental way, and like any stress it tends to suppress thyroid function. In the hypothyroid state, any estrogen which is produced tends to accumulate in the body, because of liver sluggishness.

I began to see that PMS could be controlled by certain things—extra light, supplements of sodium and magnesium, high quality protein, and correction of deficiencies of thyroid and progesterone. In working on my dissertation, I saw that tissue hypoxia (lower than optimal concentrations of oxygen in the blood) may result from estrogen excess, vitamin E deficiency, or aging. There is a close biological parallel between estrogen-dominance and the other hypoxic states, such as stress/shock, and aging.

Estrogen's Effects

As a portrait painter, I had been very conscious of the blue aspect that can often be seen in the skin of young women. In pale areas, the color may actually be blue, and in areas with a rich supply of blood, such as the lips, the color is lavender during times of high estrogen influence—around ovulation and puberty, for example. During these times of estrogen dominance, the blood is not only poorly oxygenated, but it has other special properties, such as an increased tendency to clot. The Shutes' work in the 1930s began with the use of vitamin E to antagonize estrogen's clot-promoting tendency, and led them to the discovery that vitamin E can be very therapeutic in heart disease. More recently, it has been found that men with heart disease have abnormally high estrogen,[11–14] that women using oral contraceptives have higher mortality from heart attacks,[15] and that estrogen tends to promote spasm of blood vessels.[16] (These reactions are probably related to the physiology of menstruation, in which progesterone withdrawal causes spasms in the spiral arteries of the uterus, producing endometrial anoxia and cell death.)

In toxemia of late pregnancy, or eclampsia, the exaggerated clotting tendency caused by excess estrogen (or by inadequately opposed estrogen, i.e., progesterone deficiency), can cause convulsions and strokes.

Vascular spasms could be involved here, too. The stasis caused by the vasospasm would facilitate clotting. (Vascular spasm has been observed in epilepsy, too. Epilepsy can be brought on by the premenstrual excess of estrogen, and in that situation there is no evidence that clotting is involved. Leakage of hemoglobin out of red cells can cause vasospasm, so bleeding, clotting, strokes, and seizures can interact complexly.) The brains of women who have died following eclampsia show massive clotting in the blood vessels, and their livers are characteristically injured, with clots.[4,17]

Tom Brewer and others have shown very clearly that malnutrition, especially protein deficiency, is the cause of toxemia of late pregnancy. (In Nutrition for Women, I discussed the importance of protein in allowing the liver to eliminate estrogen.)

Various researchers have demonstrated that the plaques of MS usually occur in the area served by a single blood vessel,[18–20] and some have suggested that clotting is the cause. MS patients have been found to have an abnormal clotting time, and it has been suggested that an altered diet might be able to correct the clotting tendency.

Studies in animals have shown clearly that a protein deficiency increases the fibrinogen content of blood.[21] Other factors that increase blood clotting are elevated adrenalin and cortisone. Protein deficiency causes an adaptive decrease in thyroid function, which leads to a compensatory increase in adrenaline and cortisone. The combination of high estrogen with high adrenaline increases the tendency for both clots and spasms of the blood vessels.[16]

In experimental poisoning of animals with carbon monoxide or cyanide, the brain lesions resembling MS include blood clots. The patchy distribution of these spots in the brain suggests that the clotting is secondary to metabolic damage in the brain. Presumably, the same would be true in ordinary MS, with clots and spasms being induced in certain areas by metabolic abnormalities in brain cells. The injured cells that are responsible for myelination of nerve fibers are steroid-forming cells. A failure to secrete their protective pregnenolone could cause a local spasm of a blood vessel. The circulatory problem would exacerbate the respiratory problem. Steroid production is dependent on NADH and NADPH, and so requires adequate energy supplies and energy metabolism. The phenomenon of blood-sludging, studied by M. Knisely at the University of Chicago in the l930s and l940s, is apparently a general

result of decreased energy metabolism, and is likely to be a factor in energy-and-circulatory vicious circles.

Symptoms and Therapies

Around 1976 I met a woman in her mid-thirties who heard about my work with progesterone in animals. She had been disabled by a brain disease that resembled MS or Devic's disease, inflammation of the optic nerves. It would sometimes cause blindness and paralysis that persisted for weeks at a time. During remissions, sometimes using a wheelchair, she would go to the medical school library to try to understand her condition. She came across Katherina Dalton's work with progesterone, and convinced a physician to give her a trial injection. Although she had trouble finding people who were willing to give her progesterone, her recovery was so complete that she was able to climb stairs and drive her car, and she came to my endocrinology class and gave a very good (and long) lecture on progesterone therapy. Although her sensory and motor functions became normal, she remained very fat, and chronically suffered from sore areas on her arms and legs that seemed to be abnormal blood vessels, possibly with phlebitis. She appeared to need thyroid hormone as well as larger amounts of progesterone, but never found a physician who would cooperate, as far as I know.

In the late 1970s I was seeing a lot of people who had puzzling health problems. In a period of two or three years, there were five people who had been diagnosed by neurologists as having multiple sclerosis. In talking to them, it seemed clear that they had multiple symptoms of hypothyroidism.They weren't severely disabled. Since they weren't fat or lethargic, their physicians hadn't thought they could be hypothyroid. When they tried taking a thyroid supplement, all of their symptoms disappeared, including those that had led to their MS diagnosis. One of the women went to her doctor to tell him that she felt perfectly healthy since taking thyroid, and he told her to stop taking it, because people who have MS need a lot of rest, and she wouldn't get enough rest if she was living in a normally active way. The assumption seemed to be that the diagnosis was more important than the person. (When I refer to a "thyroid supplement" I mean one that contains some T_3. Many people experience "neurological symptoms" when they take thyroxine by itself.

Experimentally, it has been found to suppress brain respiration, probably by diluting the T_3 that was already present in the brain tissue.)

Metabolism of the Oligodendrocytes

The rate-regulating step in steroid synthesis involves the entry of cholesterol into the mitochondria, where the heme-enzyme P – 450scc then removes the side-chain of cholesterol (by introducing oxygen atoms), to produce pregnenolone. This enzyme can be poisoned by carbon monoxide or cyanide, and light can eliminate the poison;[22] this could be one aspect of the winter-sickness problem.

Peripheral nerves are myelinated by essentially the same sort of cell that is called an oligodendrocyte in the brain, but outside the brain it is called a Schwann cell. It is easier to study the myelin sheath in peripheral nerves, and the electrical activity of a nerve is the most easily studied aspect of its physiology. Certain experiments seemed to indicate a "jumping" (saltatory) kind of conduction along the nerve between Schwann cells, and it was argued that the insulating function of the myelin sheath made this kind of conduction possible. This idea has become a standard item in physiology textbooks, and its familiarity leads many people to assume that the presence of myelin sheaths in the brain serves the same "insulating" function.

For a long time it has been known that heat production during nerve conduction reveals a more continuous mode of conduction, that doesn't conform to the idea of an electrical current jumping around an insulator. Even if the myelin functioned primarily to produce "saltatory conduction" in peripheral nerves, it isn't clear how this process could function in the brain. I think of the issue of "saltatory conduction at the nodes of Ranvier" as another of the fetish ideas that have served to obstruct progress in biology in the United States. A more realistic approach to nerve function can be found in Gilbert Ling's work. Ling has demonstrated in many ways that the ruling dogma of "cell membrane" function isn't coherently based on fact. He found that hormones such as progesterone regulate the energetic and structural stability of cells. Many people, unaware of his work, have felt that it was necessary to argue against the idea that there are anesthetic steroids with generalized protective functions, because of their commitment to a textbook dogma of "cell membrane" physiology.

I think the myelinating cells do have relevance to nerve conduction, but I don't think they serve primarily as electrical insulators. If the adrenal cortex were inside the heart, it would be obvious to ask whether its hormones aren't important for the heart's function. Since the oligodendrocytes are steroid-synthesizers, it seems obvious to ask whether their production of pregnenolone in response to stress or fatigue isn't relevant to the conduction processes of the nerves they surround.

Old Age

A biologist friend of mine who was about 85 became very senile. His wife started giving him thyroid, progesterone, DHEA and pregnenolone, and within a few days his mental clarity had returned. He continued to be mentally active until he was 89, when his wife interfered with his access to the hormones.

In old age the brain steroids fall to about 5 % of their level in youth. Pregnenolone and DHEA improve memory in old rats, and improve mood stability and mental clarity of old people. Pregnenolone's action in improving the sense of being able to cope with challenges probably reflects a quieting and coordinating of the "sequencing" apparatus of the forebrain, which is the area most sensitive to energy deprivation. This is the area that malfunctions in hyperactive and "dyslexic" children. Weakening of the sequencing and sorting processes probably explains the common old-age inability to extract important sounds from environmental noise, creating a kind of "confusion deafness." Insomnia, worry and "restless legs" at bedtime are problems for many old people, and I think they are variations of the basic energy-depletion problem.

The oligodendrocytes were reported[23] to be the source of the senile plaques or amyloid deposits of Alzheimer's disease.[23] Hiroisi and Lee showed the cells in different stages of degeneration, ending with translucent "mucoid" spots that stained the same as amyloid, the material in the senile plaques. This type of cell also appears to form a halo or crown around degenerating nerve cells—possibly in a protective reaction to provide the nerve cell with any pregnenolone the oligodendrocytes are able to make. The oligodendrocytes, the source of the brain steroids (that people previously believed came from the adrenals and gonads, and were just stored in the brain), myelinate nerve fibers under the influence of thyroid hormone.[24] Thyroid is responsible for both myelination and

hormone formation. In old age, glial cells become more numerous, and nerve cells become structurally and functionally abnormal, but usually there is no problem with the formation of myelin. In MS, the problem is just with myelination, and there are no senile plaques or defects in the nerve cells themselves.

These differences suggest the possibility that Alzheimer's disease involves a specific premature loss of brain pregnenolone production, but not of thyroid. Recent work suggests a central role for pregnenolone and progesterone in the regulation of consciousness,[25] and possibly in the brain's detoxifying system. Elsewhere, I have suggested that vitamin A deficiency might cause the excessive production of the "amyloid" protein. A vitamin A deficiency severely inhibits steroid synthesis. (It is used so massively in steroid synthesis that a progesterone supplement can prevent the symptoms of vitamin A deficiency.) I suspect that vitamin A is necessary for the side-chain cleavage that converts cholesterol to pregnenolone. Iron-stimulated lipid peroxidation is known to block steroid formation, and vitamin A is very susceptible to destruction by iron and oxidation. Iron tends to accumulated in tissues with aging. Gajdusek has demonstrated that brain deterioration is associated with the retention of whatever metal happens to be abundant in the person's environment, not just with aluminum. (One type of glial cell is known for its metal-binding function, causing them to be called "metallophils."). According to Gajdusek, "calcium and other di- and trivalent elements" are "deposited as hydroxyapatites in brain cells" in brain degeneration of the Alzheimer's type.[26]

Even early forms of Alzheimer's disease begin at an age when the youth-associated steroids have begun to decline. If MS involves a deficiency of thyroid (or of T_3 within the oligodendrocytes, where T_3 normally can be made from thyroxine; many things, including protein deficiency, can block the conversion of T_4 to T_3), those cells would necessarily be deficient in their ability to produce pregenolone, but in young people the brain would still be receiving a little pregnenolone, progesterone, and DHEA from the adrenals and gonads. This relatively abundant youthful supply of hormones would keep most of the body's organs in good condition, and could keep the bodies of the major brain cells from deteriorating. But if proper functioning of the nerve fibers requires that they be fed a relatively high concentration of pregnenolone from their immediately adjacent neighbors (with the amount increasing

during stress and fatigue), then their function would be impaired when they had to depend on the hormones that arrived from the blood stream.

For many years it has been recognized that the brain atrophy of "Alzheimer's disease" resembles the changes seen in the brain in many other situations: The traumatic dementia of boxers; toxic dementia; the slow-virus diseases; exposure of the brain to x-rays;[27] ordinary old age; and in people with Down's syndrome who die around the age of thirty.

In menopause, certain nerve cells have lost their ability to regulate the ovaries, because of prolonged exposure to estrogen.[6,7] The cells that fail as a result of prolonged estrogen exposure aren't the same cells that fail from prolonged exposure to the glucocorticoids,[8,9] but they have in common the factor of excitatory injury.

Since people who experience premature menopause are known to be more likely than average to die prematurely, it is reasonable to view menopause as a model of the aging process. It is now well established that progesterone fails to be produced at the onset of menopause (the first missed period, increased loss of calcium, symptoms such as hot flashes, etc.), and that estrogen continues to be produced at monthly intervals for about four years. The essential question for aging, in the present context, is why the anesthetic steroids are no longer produced at a rate that allows them to protect tissues, including brain cells, from the excitotoxins. Using menopause as a model for aging, we can make the question more answerable by asking why progesterone stops being produced.

During stress, we are designed not to get pregnant, and the simplest aspect of this is that ACTH, besides stimulating the adrenals to produce stress-related hormones, inhibits the production of progesterone by the ovary. Other stress-induced factors, such as increased prolactin and decreased thyroid, also inhibit progesterone production. Stress eventually makes us more susceptible to stress. Menopause and other landmarks of aging simply represent upward inflections in the rate-of-aging curve. Individual variations in type of stress, hormonal response and diet, etc., probably govern the nature of the aging process in an individual.

The amphetamine-like action of estrogen, which undoubtedly contributes to the general level of stress and excitotoxic abuse of nerve cells, is probably the only "useful" facet of estrogen treatment, but a little cocaine might achieve the same effect with no more harm, possibly less.

The toxicity of catecholamines has been known for over thirty years, and estrogen's stimulating effects are partly the result of its conversion to catechol-estrogens which increase the activity of brain catecholamines. Estrogen's powerful ability to nullify learning seems never to be mentioned by the people who promote its use. The importance of a good balance of brain steroids for mood, attention, memory, and reasoning is starting to be recognized, but powerful economic forces militate against its general acceptance.

Since the brain is the organ that can allow us to adapt without undergoing stress in the hormonal sense, it is very important to protect its flexibility and to keep its energy level high, so it can work in a relaxed way. It is the low energy cellular state that leads to the retention of calcium and iron, and to the production of age pigment, and other changes that constitute the vicious circle of aging. And mental activity that challenges obsession and rigidity might be the most important brain energizer. Pseudo-optimism, humor-as-therapy, has a certain value, but a deeper optimism involves a willingness to assimilate new information and to change plans accordingly.

Supplements

Nutritional supplements that might help to prevent or correct these brain syndromes include: Vitamin E and coconut oil; vitamin A; magnesium, sodium; thyroid which includes T_3; large amounts of animal protein, especially eggs; sulfur, such as magnesium sulfate or flowers of sulfur, but not to take continuously, because of sulfur's interference with copper absorption; pregnenolone; progesterone if needed. Bright light, weak in the blue end of the spectrum and with protection against ultraviolet, activates respiratory metabolism and quenches free radicals. Raw carrot fiber and/or laxatives if needed; charcoal occasionally for gas or bowel irritation. Coconut oil serves several purposes. Its butyric acid is known to increase T_3 uptake by glial cells. It has a general pro-thyroid action, for example by diluting and displacing antithyroid unsaturated oils, its short- and medium-chain fatty acids sustain blood sugar and have antiallergic actions, and it protects mitochondria against stress injury.

P.S.: In 1979, a woman whose husband was suffering from advanced Amyotrophic Lateral Sclerosis (ALS) asked me if I had any ideas for slowing his decline. I described my suspicion that ALS involved defective

metabolism or regulation of testosterone. In some tissues, testosterone is selectively concentrated to prevent atrophy, and ALS is a disease of middle-age, when hormone regulation often becomes a special problem. In the late 1970s, there was discussion of a higher incidence of ALS in males, and especially in athletes. I told her about progesterone's general protective effects, its antagonism to testosterone, and its prevention of atrophy in various tissues. She decided to ask her doctor to try progesterone for her husband. Later, I learned that her husband had gone into a very rapid decline immediately after the injection, and died within a week; the physician had given him testosterone, since, he said, "testosterone and progesterone are both male hormones." Besides making me more aware of the problems patients have in communicating with physicians, this tended to reinforce my feeling that a hormone imbalance is involved in ALS. Although I haven't written much about testosterone's toxicity, Marian Diamond's work showed that prenatal testosterone is similar to prenatal estrogen, in causing decreased thickness of the cortex of the brain; both of those hormones oppose progesterone's brain-protecting and brain-promoting actions.

Glossary

1) Amyloid is the old term for the "starchy" appearing (including the way it stains) proteins seen in various diseases, and in the brain in Alzheimer's disease.

2) Cytochrome P450scc. The cytochromes are "pigments," in the same sense that they contain the colored "heme" group that gives hemoglobin its color. P450 means "protein that absorbs light at a wavelength of 450." The scc means "side-chain cleaving," which refers to the removal of the 6 carbon atoms that distinguish cholesterol from pregnenolone. Other Cyt P450 enzymes are important for their detoxifying oxidizing action, and some of these are involved in brain metabolism.

3) Glial means "glue-like," and glial cells are mostly spidery-shaped cells that used to be thought of as just connective, supportive cells in the brain.

4) Mitochondria (the "thread-like bodies") are the structures in cells which produce most of our metabolic energy by respiration, in response to the thyroid hormones.

5) Mucoid–refers to a mucoprotein, a protein which contains some carbohydrate. A glycoprotein; usually not intended as a precise term.

6) Myelination. Myelin is a multilayered enclosure of the axons (the long processes) of nerve cells, composed of proteins and complex lipids, including cholesterol. The layered material is a flat, thin extension of the cytoplasm of the oligodendroglial cells.

7) Oligodendrocytes are one of the kinds of glial (or neuroglial) cells, and structurally they are unusual in having sheet-like, rather than just thread-like processes; they have a sensitivity ("receptors") to stress and valium, and produce pregnenolone when activated. Under the influence of thyroid hormone, they wrap themselves in thin layers around the conductive parts of nerve cells, leaving a multilayered "myelin" coating. Their absorption of thyroid hormone is promoted by butyrate, an anti-stress substance found in butter and coconut oil.

8) Steroidogenesis is the creation of steroids, usually referring to the conversion of cholesterol to hormones.

Natural Estrogens

Ray Peat's Newsletter, 2008

THE fact that an extremely large number of naturally occurring compounds, and an unlimited number of synthetic compounds, have an estrogen-like activity has been exploited by the drug companies to produce patented proprietary drugs, especially the contraceptives.

The promotion of "natural estrogens" is a new marketing strategy that capitalizes on the immense promotional investment of the drug companies in the concept of estrogen replacement as "therapy."

Estrogen marketing has entered a new phase, based on the idea of "specific estrogen-receptor modulators," the idea that a molecule can be designed which has estrogen's "good qualities without its bad qualities." This specific molecule will be "good for the bones, the heart, and the brain," without causing cancer of the breast and uterus, according to the estrogen industry. Meanwhile, soybeans are said to contain estrogens that meet that goal, and it is often said that "natural estrogens" are better than "synthetic estrogens" because they are "balanced."

Estrogen's effects on cells are immediate and profound, independent of the "estrogen receptors."

Japanese women's relative freedom from breast cancer is independent of soy products: traditional soy foods aren't the same as those so widely used in the U.S., for example, soy sauce doesn't contain the so-called soy estrogens, and tea is used much more commonly in Japan than in the U.S., and contains health protective ingredients. The "estrogenic" and "antioxidant" polyphenolic compounds of tea are not the protective agents (they raise the level of estrogen), but tea's caffeine is a very powerful and general anti-cancer protectant. The influential article in *Lancet*[2,3] used a method known to produce false results, namely, comparing the phytoestrogens (found in large amounts in soybeans) in the urine of women with or without breast cancer. For over fifty years,

> "Whether weak or strong, the estrogenic response of a chemical, if not overcome, will add extra estrogenic burden to the system. At elevated doses, natural estrogens and environmental estrogen-like chemicals are known to produce adverse effects. The source of extra or elevated concentration of estrogen could be either endogenous or exogenous. The potential of exposure for humans and animals to environmental estrogen-like chemicals is high."[1]

it has been known that the liver excretes estrogens and other toxins from the body, and that when (because of liver inertia) estrogen isn't excreted by the liver and kidneys, it is retained in the body. This process was observed in both animals and humans decades ago, and it is also well established that estrogen itself suppresses the detoxifying systems, causing fewer carcinogens to be excreted in the urine. Ingram's evidence logically would suggest that the women who have cancer are failing to eliminate estrogens, including phytoestrogens, at a normal rate, and so are retaining a higher percentage of the chemicals consumed in their diets. Flavonoids and polyphenols, like our own estrogens, suppress the detoxifying systems of the body.

Our bodies produce estrogen in a great variety of tissues, not just in the ovaries. Fat cells are a major source of it. The tendency to gain weight after puberty is one of the reasons that women's estrogen levels rise with aging throughout the reproductive years, though this isn't the basic reason for estrogen's lifelong growing influence, even in men.

Our diets provide very significant, if not always dangerous, amounts of estrogen. "Weak estrogens" generally have the full range of harmful estrogenic effects, and often have additional toxic effects. American women who eat soy products undergo changes that appear to predispose them to cancer, making their tissues even more unlike those of the relatively breast-cancer resistant Japanese than they were before eating the soy foods.

People under stress, or who have a thyroid deficiency, or who don't eat enough protein, typically have elevated estrogen levels. The accumulation of the "essential fatty acids," the polyunsaturated oils, in the tissues promotes the action of estrogen in a variety of ways, and this effect of diet tends to be cumulative, and to be self-accelerating.

Science is a method that helps us to avoid believing things that are wrong, but there is a distinct herd instinct among people who "work in science," which makes it easy to believe whatever sounds plausible, if a lot of other people are saying it is true. This is just as evident in physics as it is in medicine. Sometimes powerful economic interests help people to change their beliefs, for example as the insurance industry helped to convince the public of the dangers of smoking. Two of the biggest industries in the world, the estrogen industry and the soy bean industry, spend vast amounts of money helping people to believe certain

plausible-sounding things that help them sell their products. Sometimes they can achieve great things just by naming the substance.

Estrogenicity can be defined most simply as "acting the way estrogen does," (originally, the term "estrogen" meant "producing estrus," the female readiness to mate) and since our natural estrogen does many things, the definition is often, for practicality, based on the rapid changes produced in certain female organs by estradiol, specifically, the enlargement of the uterus by first taking up a large amount of water, and secondarily by the multiplication of cells and the production of specific proteins. A similar process occurring in the breast is also recognized as an important feature of the estrogen reaction, but as we try to define just what "estrogenicity" is, we see that there is something deeply wrong with this method of defining a hormone, because we are constantly learning more about the actions of estrogen, or of a specific form of the molecule. Calling it "the female hormone" distracted attention from its many functions in the male, and led to great confusion about its antifertility actions and its other toxicities. Many biologists called it "folliculin," because of the ovarian follicle's significant role in its production, but the pharmaceutical industry succeeded in naming it in relation to one of its functions, and then in extending that idea of it as "the producer of female receptivity" to the even more misleading idea that it is "the female hormone." But when people speak about the "estrogenicity" of a substance, they mean that it has properties that parallel those of "folliculin," the particular group of ovarian hormones that includes estradiol, estrone, and estriol.

Over the last 100 years, thousands of publications about estrogen's toxicity have created a slight resistance to the consumption of the major estrogen products. One ploy to overcoming this resistance is to call certain products "natural estrogen," as distinguished from "synthetic estrogens." The three main estrogens in our bodies are estradiol, estrone, and estriol, though there are many other minor variants on the basic molecule. These three estrogens, singly or in combinations, are being sold as natural estrogens, with their virtues explained in various ways. Implicit in many of these explanations, is the idea that these are safer than synthetics. They are sometimes contrasted to the "horse estrogen" in Premarin, as if they are better because they are like the estrogens that people produce. But it was exactly the normal human estrogens, produced by the ovaries, that led to the basic discoveries about the toxicity

of estrogen, its ability to produce cancer in any organ, to cause seizures, blood clots, birth defects, accelerated aging, etc.

Although I would suppose that a hormone from a horse might be "more natural" for a person's body than a hormone from a plant, the word "natural" as used in the phrases "natural food store," or "natural medicine," has come to be associated strongly with things derived from plants. The health food industry, now largely taken over by giant corporations to sell products that weren't producing as much revenue when sold in supermarkets and drugstores, has helped to create a culture in which botanical products are thought to be especially good and safe. Naturally grown free-range chickens used to be favored, because they could eat anything they wanted, but now eggs laid by factory chickens, eating an industrial corn-and-soy diet, are from "vegetarian chickens," because the marketers know the public will favor eggs that have the vegetarian mystique.

Biologically active molecules have both general and specific properties. Estrogenicity is a general property, but all molecules which have that property also have some other specific properties. Estriol is a little more water soluble than estrone, so it interacts with every body system in a slightly different way, entering oily environments with slightly less ease, etc.

The estrogen which occurs in yeasts, estradiol, is identical to the major human estrogen, and it is thought to have a reproductive function in yeasts, though this isn't really understood. A feature of this molecule, and of all other molecules that "act like estrogen," is the phenolic function, an oxygen and hydrogen group attached to a resonant benzene ring. Phenol itself is estrogenic, and the phenolic group is so extremely common in nature that the number of existing estrogenic substances is great, and the number of potential molecules with estrogen-function is practically infinite.

The phenolic group has many biological functions. For example, it commonly functions as an "antioxidant," though something which functions as an antioxidant in one situation is often a pro-oxidant in another situation. The molecule can have catalytic, germicidal, aromatic, neurotropic, and other functions. But it also always has, to some degree, the "estrogenic" function. This overlap of functions probably accounts for why so many plants have significant estrogenic activity.

(Natural estrogens, like other phenolics, including the flavonoids, are also mutagenic.)

The estrogenic properties of legumes were studied when sheep farmers found that their sheep miscarried when they ate clover. (I think it's interesting how this terribly toxic effect has been neglected in recent decades.) All legumes have this property, and all parts of the plant seem to contain some of the active chemicals. In beans, several substances have been found to contribute to the effect. The estrogenic effects of the seed oils and the isoflavones have been studied the most, but the well-known antithyroid actions (again, involving the oils, the isoflavones, and other molecules found in legumes) have an indirect estrogen-promoting action, since hypothyroidism leads to hyperestrogenism. (Estrogens are known to be thyroid suppressors, so the problem tends to be self-accelerating.)

The various specific actions of the many estrogenic substances in beans and other legumes haven't been throughly studied, but there is evidence that they are also—like estrogen itself—both mutagenic and carcinogenic.

The estrogen-promoting actions of soy oil apply to all of the commonly used polyunsaturated fatty acids. The same fatty acids that suppress thyroid function, have estrogenic effects.

The isoflavones (many of which are now being promoted as "antioxidants" and "cancer preventives") are toxic to many organs, but they have clear estrogenic effects, and are active not only immediately in the mature individual, but when they are present prenatally, they cause feminization of the male genitalia and behavior, and early maturation of the female offspring, with the tissue changes that are known to be associated with increased incidence of cancer.

There are interesting associations between vegetable "fiber" and estrogens. Because of my own experience in finding that eating a raw carrot daily prevented my migraines, I began to suspect that the carrot fiber was having both a bowel-protective and an antiestrogen effect. Several women who suffered from premenstrual symptoms, including migraine, had their serum estrogen measured before and after the "carrot diet," and they found that the carrot lowered their estrogen within a few days, as it relieved their symptoms.

Undigestible fiber, if it isn't broken down by bowel bacteria, increases fecal bulk, and tends to speed the transit of material through the intestine,

just as laxatives do. But some of these "fiber" materials, e.g., lignin, are themselves estrogenic, and other fibers, by promoting bacterial growth, can promote the conversion of harmless substances into toxins and carcinogens. When there is a clear "antiestrogen" effect from dietary fiber, it seems to be the result of accelerated transit through the intestine, speeding elimination and preventing reabsorption of the estrogen which has been excreted in the bile. Laxatives have this same effect on the excretion of estradiol.

Some of the isoflavones, lignins, and other phytoestrogens are said to prevent bowel cancer, but some of them, e.g., lignin, appear to sometimes increase its likelihood.

The phytoestrogens appear to pose a risk to organs besides the breast and uterus, for example the liver, colon, and pancreas, which isn't surprising, since estrogen is known to be carcinogenic for every tissue. And carcinogenesis, like precancerous changes, mutations, and reduced repair of DNA, is probably just an incidental process in the more general toxic effect of acceleration of aging.

Oils in Context

Ray Peat's Newsletter, 2006

An oil researcher[1] spent 100 days eating what he considered to be the "Eskimo diet," seal blubber and mackerel paste. He observed that his blood lipid peroxides (measured as malondialdehyde, MDA) reached a level 50 times higher than normal, and although MDA is teratogenic, he said he wasn't worried about fathering deformed children, because his sperm count had gone to zero. Evidently, he didn't have a very thorough understanding of the Eskimo way of life. In most traditional cultures, the whole animal is used for food, including the brain and the endocrine glands. Since unsaturated fats inhibit thyroid function, and since Eskimos usually have a high caloric intake but are not typically obese, it seems that their metabolic rate is being promoted by something in their diet, which might also be responsible for protecting them from the effects experienced by the oil researcher. (According to G. W. Crile, the basal metabolic rate of Eskimos was 125 % of that of people in the United States.)

People who eat fish heads (or other animal heads) generally consume the thyroid gland, as well as the brain. The brain is the body's richest source of cholesterol, which, with adequate thyroid hormone and vitamin A, is converted into the steroid hormones pregnenolone, progesterone, and DHEA, in proportion to the quantity circulating in blood in low-density lipoproteins. The brain is also the richest source of these very water-insoluble (hydrophobic) steroid hormones; it has a concentration about 20 times higher than the serum, for example. The active thyroid hormone is also concentrated many-fold in the brain.

DHEA (dehydroepiandrosterone) is known to be low in people who are susceptible to heart disease[2] or cancer, and all three of these steroids have a broad spectrum of protective actions. Thyroid hormone, vitamin A, and cholesterol, which are used to produce the protective steroids, have been found to have a similarly broad range of protective effects, even when used singly. For example, according to MacCallum,

It has been shown that certain lipoid substances, especially cholesterine, can act as inhibiting or neutralizing agents toward such haemolytic poisons as saponin, cobra poison, etc., through forming with them an innocuous compound. Hanes showed that the relative immunity

of puppies from chloroform poisoning is due to the large amount of cholesterin esters in their tissues. When artificially introduced into the tissues of adult animals a similar protection is conferred.[3]

A high level of serum cholesterol is practically diagnostic of hypothyroidism, and can be seen as an adaptive attempt to maintain adequate production of the protective steroids. Broda Barnes' work clearly showed that hypothyroid populations are susceptible to infections, heart disease, and cancer.[4]

In the 1940s, some of the toxic effects of fish oil (such as testicular degeneration, softening of the brain, muscle damage, and spontaneous cancer) were found to result from an induced vitamin E deficiency. Unfortunately, there isn't much reason to think that just supplementing vitamin E will provide general protection against the unsaturated fats. The half-life of fats in human adipose tissue is about 600 days, meaning that significant amounts of previously consumed oils will still be present up to four years after they have been removed from the diet.[5] According to Draper, et al.,[6] enrichment of the tissues with highly unsaturated fatty acids results in an increase in lipid peroxidation *in vivo* even in the presence of normal concentrations of vitamin E. Fasting for more than 24 hours also results in an increase in MDA excretion, implying that lipolysis is associated with peroxidation of the fatty acids released.

According to Lemeshko, et al., it seems that this effect increases with the age of the animal.[7]

Commercial advertising (including medical conferences sponsored by pharmaceutical companies) and commercially sponsored research are creating some false impressions about the role of unsaturated oils in the diet. Like the man who poisoned himself with the "Eskimo diet," many people focus so intently on avoiding one problem that they create other problems. Since I have discussed the association of unsaturated fats with aging, lipofuscin, and estrogen elsewhere, I will outline some of the other problems associated with the oils, especially as they relate to hormones.

Mechanisms and Essentiality: When something is unavoidable, in ordinary life, talking about "essentiality," or the minimum amount required for life or for optimal health, is more important as an exploration into the nature of our life than as a practical health issue. For example, how much oxygen, how many germs (of what kinds), how many cosmic rays (of what kinds), would produce the nicest human beings? The fact

that we have adapted to something—oxygen at sea level, microbes, or vegetable fats, for example—doesn't mean that we are normally exposed to it in ideal amounts.

Animals contain desaturase enzymes, and are able to produce specific unsaturated fats (from oleic and palmitoleic acids) when deprived of the ordinary "essential fatty acids,"[8] so it can be assumed that these enzymes have a vital purpose. The high concentration of unsaturated fats in mitochondria—the respiratory organelles where it seems that these lipids present a special danger of destructive oxidation—suggests that they are required for mitochondrial structure, or function, or regulation, or reproduction. Unsaturated fats have special properties of adsorption,[8] and are more soluble in water than are saturated fats. The movement and modulation of proteins and nucleic acids might require these special properties. As the main site of ATP production, I suspect that their water-retaining property might be crucial. When a protein solution (even egg-white) is poured into a high concentration of ATP, it contracts or "superprecipitates." This condensing, water-expelling property of ATP in protein solutions is similar to the effect of certain concentrations of salts on any polymer. It would seem appropriate to have a substance to oppose this condensing effect, to stimulate swelling[9,10] and the uptake of precursor substances. Something that has an intrinsic structure-loosening or water-retaining effect would be needed. The ideas of "chaotropic agents" and "structural antioxidants" have been proposed by Vladimirov[11] to bring generality into our understanding of the mitochondria. Lipid peroxides are among the chaotropic agents, and thyroxin is among the structural antioxidants. The known oxygen-sparing effects of progesterone[12,13] would make it appropriate to include it among the structural antioxidants. The incorporation of the wrong unsaturated fats into mitochondria would be expected to damage the vital respiratory functions.

Some insects that have been studied have been found not to require the essential fatty acids.[14†] According to reviewers, hogs and humans have not been shown to require the "essential" fatty acids.[15] *In vitro* studies indicate that they are not required for human diploid cells to continue dividing in culture.[16] According to Guarnieri,[8] EFA-deficient animals don't die from their deficiency. The[8] EFA-deficient animals don't die from their deficiency. The early studies showing "essentiality" of unsaturated fats, by producing skin problems and an increased metabolic

rate, have been criticized[17] in the light of better nutritional information, e.g., pointing out that the diets might have been deficient in vitamin B_6 and/or biotin. The similar skin condition produced by vitamin B_6 deficiency was found to be improved by adding unsaturated fats to the diet. A fat-free liver extract cured the "EFA deficiency." I think it would be reasonable to investigate the question of the increased metabolic rate produced by a diet lacking unsaturated fats (which inhibit both thyroid function and protein metabolism) in relation to the biological changes that have been observed. Since diets rich in protein are known to increase the requirement for vitamin B_6[18] (which is a co-factor of transaminases, for example), the increased rate of energy production and improved digestibility of dietary protein on a diet lacking unsaturated fats would certainly make it reasonable to provide the experimental animals with increased amount of other nutrients. With increasing knowledge, the old experiments indicating the "essentiality" of certain oils have lost their ability to convince, and they haven't been replaced by new and meaningful demonstrations. In the present state of knowledge, I don't think it would be unreasonable to suggest that the optional dietary level of the "essential fatty acids" might be close to zero, if other dietary factors were also optimized. The practical question, though, has to do with the dietary choices that can be made at the present time.

In evaluating dietary fat, it is too often forgotten that the animals' diet (and other factors, including temperature) affect the degree of saturation of fats in its tissues, or its milk, or eggs. The fat of wild rabbits or summer-grazing horses, for example, can contain 40 % linolenic acid, about the same as linseed oil. Hogs fed soybeans can have fat containing over 30 % linoleic acid.[19] Considering that most of our food animals are fed large amounts of grains and soybeans, it isn't accurate to speak of their fats as "animal fats." And, considering the vegetable oil contained in our milk, eggs, and meat, it would seem logical to select other foods that are not rich in unsaturated oils.

Temperature and Fat: The fact that saturated fats are dominant in tropical plants and in warm-blooded animals relates to the stability of these oils at high temperatures. Coconut oil which had been stored at

[†] If we followed Linus Pauling's reasoning in determining optimal vitamin C intake, this study of the linoleic acid content of the tissues of an animal which can synthesize it would suggest that we are eating about 100 times more "EFA" than we should.

room temperature for a year was found to have no measurable rancidity. Since growing coconuts often experience temperatures around 100 °F, ordinary room temperature isn't an oxidative challenge. Fish oil or safflower oil, though, can't be stored long at room temperature, and at 98 °F, the spontaneous oxidation is very fast.

Bacteria vary the kind of fat they synthesize, according to temperature, forming more saturated fats at higher temperatures.[20] The same thing has been observed in seed oil plants.[21] Although sheep have highly saturated fat, the superficial fat near their skin is relatively unsaturated; it would obviously be inconvenient for the sheep if their surface fat hardened in cool weather, when their skin temperature drops considerably. Pigs wearing sweaters were found to have more saturated fat than other pigs.[22] Fish, which often live in water which is only a few degrees above freezing, couldn't function with hardened fat. At temperatures which are normal for fish, and for seeds which germinate in the cold northern springtime, rancidity of fats isn't a problem, but rigidity would be.

Unsaturated Fats Are Essentially Involved In Heart Damage: The toxicity of unsaturated oils for the heart is well established,[23–25] though not well known by the public.

In 1962, it was found that unsaturated fatty acids are directly toxic to mitochondria.[26] Since stress increases the amount of free fatty acids circulating in the blood (as well as lipid peroxides), and since lack of oxygen increases the intracellular concentration of free fatty acids, stored unsaturated fats would seem to represent a special danger to the stressed organism. Meerson and his colleagues[17] have demonstrated that stress liberates even local tissue fats in the heart during stress, and that systematic drug treatment, including antioxidants, can stop the enlargement of stress-induced infarctions. Recently, it was found that the cardiac necrosis caused by unsaturated fats (linolenic acid, in particular) could be prevented by a cocoa butter supplement.[27] The author suggests that this is evidence for the "essentiality" of saturated fats, but points out that animals normally can produce enough saturated fat from dietary carbohydrate or protein, to prevent cardiac necrosis, unless the diet provides too much unsaturated fat. A certain proportion of saturated fat appears to be necessary for stability of the mitochondria. Several other recent studies show that the "essential" fatty acids decrease the P/O ratio, or the phosphorylation efficiency,[28,29] the amount of usable energy produced by cellular respiration.

There has been some publicity about a certain unsaturated fat, eicosapentaenoic acid, or EPA, which can have some apparently protective and anti-inflammatory effects. A study in which butter was added to the animals' diet found that serum EPA was elevated by the butter. The investigator pointed out that other studies had been able to show increased serum EPA from an EPA supplement only when the animals had previously been fed butter.[30]

Intense lobbying by the soybean oil industry has created the widespread belief that "tropical oils" cause heart disease. In a comparison of many kinds of oil, including linseed oil, olive oil, whale oil, etc., palm oil appeared to be the most protective. The same researcher[31,32] more recently studied palm oil's antithrombotic effect, in relation to platelet aggregation. It was found that platelet aggregation was enhanced by sunflowerseed oil, but that palm oil tended to decrease it.

Much current research has concentrated on the factors involved in arterial clotting. Since the blood moves quickly through the arteries, rapid processes are of most interest to those workers, though some people do remember to think in terms of an equilibrium between formation and removal of clot material. For about 25 years there was interest in the ability of vitamin E to facilitate clot removal, apparently by activating proteolytic enzymes.[33] Unsaturated fats' ability to inhibit proteolytic enzymes in the blood has occasionally been discussed, but seldom in the U.S. The equilibrium between clotting and clot dissolution is especially important in the veins, where blood moves more slowly, and spends more time.

...The slower blood flows the greater its predisposition to clotting. However, this intrinsic process, leading to fibrin production, is slow, taking up to a minute or more to occur. Thrombosis as a result of stasis, therefore, occurs in the venous circulation; typically in the legs where...venous return is slowest. In fact, many thousands of small thrombi are formed each day in the lower body. These pass via the vena cava into the lungs where thrombolysis occurs, this being a normal metabolic function of the organ.[34]

In the Shutes' research in the 1930s and 1040s, vitamin E and estrogen acted in opposite directions on the clot-removing enzymes.[33] Since estrogen increases blood lipids, and increases the incidence of strokes and heart attacks, it would be interesting to expand the Shutes' work by considering the degree of saturation of blood lipids in relation to the

effects of vitamin E and estrogen on clot removal. Estrogen's effect on clotting is very complex, since it increases the ratio of unsaturated to saturated fatty acids in the body, and increases the tendency of blood to pool in the large veins, in addition to its direct effects on the clotting factors.

Immunodeficiency and Unsaturated Fats: Intravenous feeding with unsaturated fats is powerfully immunosuppressive[35] (though it often was used to give more calories to cancer patients) and is now advocated as a way to prevent graft rejection. The deadly effect of the long-chain unsaturated fats on the immune system has led to the development of new products containing short and medium-chain saturated fats for intravenous feeding.[36] It was recently reported that the anti-inflammatory effect of n-3 fatty acids (fish oil) might be related to the observed suppression of interleukin-1 and tumor necrosis factor by those fats.[37] The suppression of these anti-tumor immune factors persists after the fish oil treatment is stopped.

As mentioned above, stress and hypoxia can cause cells to take up large amounts of fatty acids. Cortisol's ability to kill white blood cells (which can be inhibited by extra glucose) is undoubtedly an important part of its immunosuppressive effect, and this killing is mediated by causing the cells to take up unsaturated fats.[38]

Several aspects of the immune system are improved by short-chain saturated fats. Their anti-histamine action[39] is probably important, because of histamine's immunosuppressive effects.[40] Unsaturated fats have been found to cause degranulation of mast cells.[41] The short-chain fatty acids normally produced by bacteria in the bowel apparently have a local anti-inflammatory action.[42]

A recent discussion of "tissue destruction by neutrophils" mentions "a fascinating series of experiments performed between 1888 and 1906," in which "German and American scientists established the importance of neutrophil proteinases and plasma antiproteinases in the evolution of tissue damage *in vivo*."[43] MacCallum's Pathology described some related work:

...Jobling has shown that the decomposition products of some fats—unsaturated fatty acids and their soaps—have the most decisive inhibiting action upon proteolytic ferments, their power being in a sense proportional to the degree of unsaturation of the fatty acid. So universally is it true that such unsaturated fatty acids can impede the action of

proteolytic ferments that many pathological conditions (such as the persistence of caseous tuberculous material in its solid form) can be shown to be due to their presence. If they are rendered impotent by saturation of their unsaturated group with iodine, the proteolysis goes on rapidly and the caseous tubercle or gumma rapidly softens.[3]

Another comment by MacCallum suggests one way in which unsaturated fats could block the action of cytotoxic cells:

This function of the wandering cells is, of course, of immediate importance in connection with their task of cleaning up the injured area to prepare it for repair. While the proteases thus produced are active in the solution of undesirable material, their unbridled action might be detrimental. As a matter of fact, it is shown by Jobling and Petersen that the anti-ferment known to be present in the serum and to restrict the action of the ferment is a recognizable chemical substance, usually a soap or other combination of an unsaturated fatty acid. It is possible to remove or decompose this substance or to saturate the fatty acid with iodine and thus release the ferment to its full activity.[3]

Unsaturated Fats Are Essential For Cancer: The inhibition of proteolytic enzymes by unsaturated fats will act at many sites: digestion of protein, "digestion" of clots, "digestion" of the colloid in the thyroid gland which releases the hormones, the activity of white cells mentioned above, and the normal "digestion" of cytoplasmic proteins involved in maintaining a steady state as new proteins are formed and added to the cytoplasm. It has been suggested that inhibition of the destruction of intracellular proteins would shift the balance toward growth.[44] Cancer cells are known to have a high level of unsaturated fats,[45] yet they have a low level of lipid peroxidation;[46,47] lipid peroxidation inhibits growth, and is often mentioned as a normal growth restraining factor.[11,48,49]

In 1927, it was observed that a diet lacking fats prevented the development of spontaneous tumors.[50] Many subsequent investigators have observed that the unsaturated fats are essential for the development of tumors.[51–53] Tumors secrete a factor which mobilizes fats from storage,[54] presumably guaranteeing their supply in abundance until the adipose tissues are depleted. Saturated fats—coconut oil and butter, for example—do not promote tumor growth.[55,56] Olive oil is not a strong tumor promoter, but in some experiments it does have a slightly permissive effect on tumor growth.[57,58] In some experiments, the carcinogenic action of unsaturated fats could be offset by added

thyroid,[58] an observation which might suggest that at least part of the effect of the oil is to inhibit thyroid. Adding cystine to the diet (cysteine, the reduced form of cystine, is a thyroid antagonist) also increases the tumor incidence.[59] In a hyperthyroid state, the ability to quickly oxidize larger amounts of the toxic oils would very likely have a protective effect, preventing storage and subsequent peroxidation, and reducing the oils' ability to synergize with estrogen.

Consumption of unsaturated fat has been associated with both skin aging and with the sensitivity of the skin to ultraviolet damage, Ultraviolet light-induced skin cancer seems to be mediated by unsaturated fats and lipid peroxidation.[60]

In a detailed study of the carcinogenicity of different quantities of unsaturated fat, Ip, et al., tested levels ranging from 0.5 % to 10 %, and found that the cancer incidence varied with the amount of "essential oils" in the diet. Some of their graphs make the point very clearly:[52]

This suggests that the optimal EFA intake might be 0.5 % or less.

Butter and coconut oil contain significant amounts of the short and medium-chain saturated fatty acids, which are very easily metabolized,[61] inhibit the release of histamine,[39] promote differentiation of cancer cells,[62] tend to counteract the stress-induced proteins,[63] decrease the expression of prolactin receptors, and promote the expression of the T_3 (thyroid) receptor.[64] (A defect of the thyroid receptor molecule has been identified as an "oncogene," responsible for some cancers, as has a defect in the progesterone receptor.)

Besides inhibiting the thyroid gland, the unsaturated fats impair intercellular communication,[65] suppress several immune functions that relate to cancer, and are present at high concentrations in cancer cells, where their antiproteolytic action would be expected to interfere with the proteolytic enzymes and to shift the equilibrium toward growth. In the free fatty acid form, the unsaturated fats are toxic to the mitochondria, but cancer cells are famous for their compensatory glycolysis.

By using lethargic connective tissue cells known to have a very low propensity to take up unsaturated fats[66] as controls in comparison with, e.g., breast cancer cells, with a high affinity for fats, it is possible to show a "selective" toxicity of oils for cancer cells. However, an *in vivo* test of an alph-linolenic acid ester showed it to have a stimulating effect on breast cancer.[67] Given a choice, skin fibroblasts demonstrate a very specific preference for oleic acid, over a polyunsaturated fat.[68]

Even if unsaturated fats were (contrary to the best evidence) selectively toxic for cancer cells, their use in cancer chemotherapy would have to deal with the issues of their tendency to cause pulmonary embolism,their suppression of immunity including factors specifically involved in cancer resistance, and their carcinogenicity.

Brain Damage And Lipid Peroxidation: When pregnant mice were fed either coconut oil or unsaturated seed oil, the mice that got coconut oil had babies with normal brains and intelligence, but the mice exposed to the unsaturated oil had smaller brains, and had inferior intelligence. In another experiment, radioactively labeled soy oil was given to nursing rats, and it was shown to be massively incorporated into brain cells, and to cause visible structural changes in the cells. In 1980, shortly after this study was published in Europe, the U.S. Department of Agriculture issued a recommendation against the use of soy oil in infant formulas. More recently,[69] pregnant rats and their offspring were given soy lecithin with their food, and the exposed offspring developed sensorimotor defects.

Many other studies have demonstrated that excessive unsaturated dietary fats interfere with learning and behavior,[70–73] and the fact that some of the effects can be reduced with antioxidants suggests that lipid peroxidation causes some of the damage. Other studies are investigating the involvement of lipid peroxidation in seizures.[74]

The past use of soy oil in artificial milk (and in maternal diets) has probably caused some brain damage. The high incidence of neurological defects (e.g., 90 %) that has been found among violent criminals suggests that it might be worthwhile to look for unusual patterns of brain lipids in violent people.

There have been a series of claims that babies' brains or eyes develop better when their diets are supplemented with certain unsaturated oils, based on the idea that diets may be deficient in certain types of oil, Some experimenters claim that the supplements have improved the mental development of babies, but other researchers find that the supplemented babies have poorer mental development. But the oils that are added to the babies' diets are derived from fish or algae, and contain a great variety of substances (such as vitamins) other than the unsaturated fatty acids, and the researchers consistently fail to control for the effects of such substances.

It has been shown that it is probably impossible to experience a detectable deficiency of linoleic acid outside of the laboratory setting,[75] but the real issue is probably whether the amount in the normal diet is harmful to development. Until the research with animals has produced a better understanding of the effects of unsaturated oils, experimenting on human babies seems hard to justify.

Marion Diamond, who has studied the improved brain growth in rats given a stimulating environment (which, like prenatal progesterone, produced improved intelligence and larger brains), observed that in old age the "enriched" rats' brains contained less lipofuscin (age pigment).[12] It is generally agreed that the unsaturated oils promote the formation of age pigment. The discovery that stress or additional cortisone (which, by blocking the use of glucose, forces cells to take up more fat) causes accelerated aging of the brain[76] should provide new motivation to investigate the antistress properties of substances such as the protective steroids mentioned above, and the short-chain saturated fats.

Essential for Liver Damage: Both experimental and epidemiological studies have shown that dietary linoleic acid is required for the development of alcoholic liver damage.[77] Animals fed tallow and ethanol had no liver injury, but even 0.7 % or 2.5 % linoleic acid with ethanol caused fatty liver, necrosis, and inflammation. Dietary cholesterol at a level of 2 % was found to cause no harm,[78] but omitting it entirely from the diet caused leakage of amino-transferase enzymes. This effect of the absence of cholesterol was very similar to the effects of the presence of linoleic acid with ethanol.

Obesity: For many years studies have been demonstrating that dietary coconut oil causes decreased fat synthesis and storage, when compared with diets containing unsaturated fats. More recently, this effect has been discussed as a possible treatment for obesity.[79] The short-chain fats in coconut oil probably improve tissue response to the thyroid hormone (T_3), and its low content of unsaturated fats might allow a more nearly optimal function of the thyroid gland and of mitochondria. A survey of other tropical fruits' content of short and medium chain fatty acids might be useful, to find lower calorie foods which contain significant amounts of the shorter-chain fats.

Other Problem Areas: The presence of palmitate in the lung surfactant phospholipids[80] suggests that maternal overload with unsaturated fats might interfere with the formation of these important substances,

causing breathing problems in the newborn. The bone-calcium mobilizing effect of prostaglandins suggests that dietary fats might affect osteoporosis; the absence of osteoporosis in some tropical populations might relate to their consumption of coconut oil and other saturated tropical oils. The steroids which occur in association with some seed oils might be nutritionally significant, in the way animal hormones in foods undoubtedly are. For example, soy steroids can be converted by bowel bacteria into estrogens. R. Marker, et al., found diosgenin (the material in the Mexican yam from which progesterone, etc., are derived) in a palm kernel, Balanites aegyptica (Wall).[81] Another palm fruit also contains sterols with anti-androgenic and anti-edematous actions.[82,83]

If the amount of ingested unsaturated fats (inhibitors of protein digestion) were lower, protein requirements might be lower.

The similar effects of estrogen and of polyunsaturated fats (PUFA) are numerous. They include antagonism to vitamin E and thyroid, to respiration and proteolysis; promotion of lipofuscin formation and of clot formation, promotion of seizure activity, impairment of brain development and learning; and involvement in positive or negative regulation of cell division, depending on cell type.

These parallels suggest that the role of PUFA in reproduction might be similar to that of estrogen, namely, the promotion of uterine and breast cell proliferation, water uptake, etc. Such parallels should be a caution in generalizing from the conditions which are essential for reproduction to the conditions which are compatible with full development and full functional capacity. If a certain small amount of dietary PUFA is essential for reproduction, but for no other life function, then it is analogous to the brief "estrogen surge," which must quickly be balanced by opposing hormones. The present approach to contraception through estrogen-induced miscarriage might give way to fertility regulation by diet. A self-actualizing pro-longevity diet, low in PUFA, might prolong our characteristically human condition of delayed reproductive maturity, and, if PUFA are really essential for reproduction, unsaturated vegetable oils could temporarily be added to the diet when reproduction is desired.

Conclusions

Polyunsaturated fats are nearly ubiquitous, but if they are "essential nutrients," in the way vitamin A, or lysine, is essential, that has not been

demonstrated. It seems clear that they are essential for cancer, and that they have other properties which cause them to be toxic at certain levels. It might be time to direct research toward determining whether there is a threshold of toxicity, or whether they are, like ionizing radiation, toxic at any level.

Note

A possible mitochondrial site for toxicity: In 1971 I was trying to combine some of the ideas of Albert Szent-Györgyi, Otto Warburg, W. F. Koch, and L. C. Strong. I was interested in the role of ubiquinone in mitochondrial respiration. In one experiment, I was using paper chromatography to compare oils that I had extracted from liver with vitamin E and with commercially purified ubiquinone. Besides using the pure substances, I decided to combine vitamin E with ubiquinone for another test spot. As soon as I combined the two oils, their amber and orange colors turned to an inky, greenish black color. I tested both bacterial and mammalian ubiquinone, and benzoquinone, and they all produced similar colors with vitamin E. When I ran the solvent up the paper, the vitamin E and the ubiquinone traveled at slightly different speeds. The black spot, containing the mixture, also moved, but each substance moved at its own speed, and as the materials separated, their original lighter colors reappeared. Charge-transfer bonds, which characteristically produce dark colors, are very weak bonds. I think this must have been that kind of bond. Years later, I tried to repeat the experiment, using "ubiquinone" from various capsules that were sold for medical use. Instead of the waxy yellow-orange material I had used before, these capsules contained a liquid oil with a somewhat yellow color. Very likely, the ubiquinone was dissolved in vegetable oil. At the time, I was puzzled that the color reaction didn't occur, but later I realized that a solvent containing double bonds (e.g., soy oil or other oil containing PUFA) would very likely prevent the close association between vitamin E and ubiquinone which is necessary for charge-transfer to occur. Since I think Koch and Szent-Györgyi were right in believing that electronic activation is the most important feature of the living state, I think the very specific electronic interaction between vitamin E and ubiquinone must play an important role in the respiratory function of ubiquinone. Ubiquinone is known to be a part of the electron transport chain which can leak electrons, so this

might be one of the ways in which vitamin E can prevent the formation of toxic free-radicals.[84] If it can prevent the "leakage" of electrons, then this in itself would improve respiratory efficiency. If unsaturated oils interfere with this very specific but delicate bond, then this could explain, at least partly, their toxicity for mitochondria.

Osteoporosis, Aging, Tissue Renewal, and Product Science

Ray Peat's Newsletter, 2012

THE incidence of osteoporosis, like obesity, has been increasing in recent decades. The number of hip fractures in many countries has doubled in the last 30 or 40 years.[1] An exception to that trend was Australia in the period between 2001 and 2006, where the annual incidence of hip fractures in women over 60 years old decreased by 28.3 %. During those years, the number of prescriptions for "hormone replacement therapy" decreased by 54.6 %, and the number of prescriptions for bisphosphonate increased by 245 %. The publication of the Women's Health Initiative results in 2002 (showing that the Prem-Pro treatment caused breast cancer, heart attacks, and dementia), led to a great decrease in the use of estrogen treatments everywhere.

After the FDA approved estrogen's use in 1972 for the prevention of osteoporosis the number of women using it increased greatly, and by 1994, 44 % of women in the U.S. had used it. After the WHI results were published, the number of prescriptions for "HRT" fell by more than half, and following that decrease in estrogen sales, the incidence of breast cancer decreased by 9 % in women between the ages of 50 and 54.

With the incidence of hip fractures increasing while the percentage of women using estrogen was increasing, it seems likely that there is something wrong with the theory that osteoporosis is caused by an estrogen deficiency. That theory was derived from the theory that menopause was the consequence of ovarian failure, resulting from the failure to ovulate and produce estrogen when the supply of eggs was depleted. The theory was never more than an ideological preference, but the estrogen industry saw it as an opportunity to create a huge market.

There are many studies that seem to imply that the greater incidence of osteoporotic fractures among women is the result of their exposure to estrogen during their reproductive years. This would be analogous to the understanding that it is the cumulative exposure to estrogen that ages the nerves in the hypothalamus that control the cyclic release of the gonadotropic hormones, causing the menopause.

The nature of science itself changed around the middle of the last century, becoming product and disease oriented, so that now relatively few people are continuing to study bones objectively.

Animal studies show that estrogen stunts growth, including bone growth. The high estrogen levels in girls' teen years and early twenties accounts for the fact that women's bones are lighter than men's. In rat studies, treatment with estrogen was found to enlarge the space between the jawbone and the teeth, which is a factor in periodontal disease.[2] Teeth are very similar to bones, so it's interesting that treating male or female rats with estrogen increases their incidence of tooth decay, and removing their gonads was found to decrease the incidence.[3] Supplementing them with thyroid hormone decreased the incidence of cavities in both males and females.[4]

One of the "estrogen receptors" appears to actively contribute to bone loss.[5,6] Studies in dogs following the removal of their ovaries found that there was an increase of bone remodeling and bone formation rate in the first month, followed by a few months of slowed bone formation, but that by 10 months after the surgery the bones had returned to their normal remodeling rate, and that "at no time was a significant reduction in bone volume detected".[7] With the removal of the ovaries, the production of progesterone as well as estrogen is affected, but the adrenal glands and other tissues can produce those hormones.

Until the influence of the estrogen industry overwhelmed it, ordinary science was studying bone development in comprehensive ways, understanding its biological roles and the influences of the environment on it. But the nature of science itself changed around the middle of the last century, becoming product and disease oriented, so that now relatively few people are continuing to study bones objectively.

The outstanding physical-chemical property of bone is that it is a reservoir-buffer of carbon dioxide, able to bind huge amounts of the gas into its structure.

When carbon dioxide increases in the bloodstream it is at first absorbed rapidly by the bones, and if the blood level of CO_2 is kept high day after day, the rate of absorption gradually slows down, but in experiments that have continued for several weeks the bones were still slowly absorbing more carbon dioxide; the absorption curve seems to be asymptotic. When people move to or from high altitudes, their bones appear to continue adapting to the different gas pressures for years. A reduction

of atmospheric pressure (which allows the tissues to retain more carbon dioxide) helps to reduce the calcium loss caused by immobility,[8,9] and promotes the healing of damaged bone.[10] Ultrasound treatment, which accelerates bone healing, stimulates processes similar to reduced oxygen supply.[11]

The mineral in newly formed bone is calcium carbonate, and this is gradually changed to include a large amount of calcium phosphate. Besides forming part of the mineral, carbon dioxide is also incorporated into a protein (in a process requiring vitamin K), in a process that causes this protein, osteocalcin, to bind calcium. The osteocalcin protein is firmly bonded to a collagen molecule. Collagen forms about 30 % of the mass of bone; several percent of the bone consists of other organic molecules, including osteocalcin, and the rest of the mass of the bone consists of mineral.

Thyroid hormone is essential for forming carbon dioxide. In the early 1940s, experimental rabbits were fed their standard diet, with the addition of 1 % desiccated thyroid gland, which would be equivalent to about 150 grains of Armour thyroid for a person. They became extremely hypermetabolic, and couldn't eat enough to meet their nutritional needs for growth and tissue maintenance. When they died, all of their tissues weighed much less than those of animals that hadn't received the toxic dose of thyroid, except for their bones, which were larger than normal. Experiments with the thin skull bones of mice have shown that the active thyroid hormone, T_3, increases the formation of bone. To increase cellular respiration and carbon dioxide production, T_3 increases the activity of the enzyme cytochrome oxidase, which uses copper as a co-factor. Increased thyroid activity increases the absorption of copper from foods.

There is an inherited condition in humans, called osteopetrosis or marble bone disease, caused by lack of a carbonic anhydrase enzyme, which causes them to retain a very high level of carbon dioxide in their tissues. Using a chemical that inhibits carbonic anhydrase, such as the diuretic acetazolamide, a similar condition can be produced in animals. Acetazolamide inhibits the bone resorbing actions of parathyroid hormone, including lactic acid formation and the release of the lysosomal enzyme, beta-glucuronidase.[12]

While lactic acidosis causes bone loss, acidosis caused by increased carbonic acid doesn't; low bicarbonate in the body fluids seems to remove

carbonate from the bone,[13] and also mineral phosphates.[14] The parathyroid hormone, which removes calcium from bone, causes lactic acid to be formed by bone cells.[15,16] Lactic acid produced by intense exercise causes calcium loss from bone,[17] and sodium bicarbonate increases calcium retention by bone. Vitamin K_2[18] blocks the removal of calcium from bone caused by parathyroid hormone and prostaglandin E_2, by completely blocking their stimulation of lactic acid production by bone tissues. Aspirin, which, like vitamin K, supports cell respiration and inhibits lactic acid formation, also favors bone calcification. Vitamin K_2 stimulates the formation of two important bone proteins, osteocalcin and osteonectin,[19] and reduces the activity of estrogen by oxidizing estradiol.[20]

The formation of eggshell, which is mostly calcium carbonate, is analogous to the early stage of bone formation. In hot weather, when chickens pant and lower their carbon dioxide, they form thin shells. A sodium bicarbonate supplement improves the quality of the eggshell.[21,22] Chickens that habitually lay eggs with thinner shells have lower blood bicarbonate than those that lay thick shelled eggs.[23]

One of the arguments for stopping the sale of DDT in the U.S. was that it was threatening to cause extinction of various species of bird because it caused them to lay eggs with very weak shells. Several other synthetic estrogenic substances, ethynylestradiol, lindane, PCBs, cause eggshell thinning, partly by altering carbonic anhydrase activity.[24] Estrogen and serotonin activate carbonic anhydrase in some tissues, progesterone tends to inhibit it. DDE, a metabolite of DDT, reduces medullary bone formation in birds[25] and bone mineral density in men.[26] Among its estrogenic effects, DDE increases prolactin;[27] one form of DDT inhibits progesterone synthesis and increases estrogen[28]

In youth, the mineralization of the collagen framework is slightly lower than in maturity, and the bones are more flexible. With aging, the mineralization increases progressively, and the proportion of collagen decreases slightly, and the bones become increasingly brittle.[29,30]

Collagen is a major part of the extracellular substance everywhere in the body, and its concentration increases with aging in the non-calcified tissues. There is considerable renewal and modification of collagen, as new molecules are formed and old molecules broken down, but its average structure changes with aging, becomes less soluble and more rigid, as the result of chemical cross-links formed between molecules.

These cross-links are involved in regulating the differentiation of bone cells.[31] Recently (August 2, 2011), Deasey et al., have published evidence showing that cross-linking is required for bone mineralization (2011).

The outstanding physical-chemical property of bone is that it is a reservoir-buffer of carbon dioxide, able to bind huge amounts of the gas into its structure.

Around 1950, Fritz Verzar began studying the changes of collagen that occur with aging, and his work led to the "collagen theory of aging." He showed that older, stiffer, less elastic tendons have a higher "melting" or contracting temperature than young tendons. (This effect is responsible for the curling of a piece of meat when it is frying.)

Verzar and his colleagues investigated the effects of hormonal treatments on the aging of rat collagen, especially in their tail tendons. They found that estrogen treatment increased the stiffness and the melting temperature of collagenous tissues. While estrogen increased the cross-linking with aging, removing the pituitary gland was found to retard the aging.

Later, the cross-linking enzymes transglutaminase and lysyl oxidase, which are induced by estrogen, were found to be a major factor in the cross-linking of collagen and other molecules.

When estrogen was found to age the connective tissues, it was assumed that continual breeding during an animal's life-time, greatly increasing the total exposure of the tissues to estrogen, would increase the aged rigidity of the connective tissues, but these animals were found to have less rigid tissues. During pregnancy other hormones, especially progesterone, were also increased, and it was suggested that this reversed the effects of aging and estrogen. Since most people had believed that frequent pregnancies would cause a woman to age more rapidly, a large survey of records was done, to compare the longevity of women with the number of pregnancies. It was found, in the very extensive Hungarian records, that life-span was increased in proportion to the number of pregnancies.

Despite these very interesting results in the 1950s and 1960s, the growing influence of the estrogen industry changed the direction of aging research, favoring the belief that decreasing estrogen accelerated the deterioration of tissues in aging, and the popularity of Denham Harman's "free radical theory of aging" led many people to assume that random reactions produced by lipid peroxidation were responsible for

most of the cross-linking, and that theory was gradually replaced by the "glycation" theory of aging, in which sugar molecules break down and form the cross-links, by random, non-enzymic processes. Estrogen's role in aging was completely by-passed.

The meat industry is interested in reducing the toughness of meat, by influencing the nature of the collagen in muscle. Castrated animals were found to produce meat that was tenderer than that of intact males. When castrated animals were treated with testosterone, the amount of collagen was increased, making the meat tougher. But when dihydrotestoserone, which can't be converted to estrogen was used, the meat didn't become tough. Treatment with estrogen produced the same increase of collagen as treatment with testosterone, showing that testosterone's effect was mainly the result of its conversion to estrogen.[32]

In the 1960s and '70s the estrogen industry was looking for ways to build on the knowledge that in puberty estrogen is responsible for accelerating the calcification of the growth plate at the ends of the long bones, and to find a rationale for selling estrogen to all women concerned with the problems of aging. As bone metabolism was investigated, two kinds of cell were found to be active in constantly remodeling the bone structure: Osteoclasts (breaking it down), and osteoblasts (building new bone). Estrogen was found to slow the actions of the osteoclasts, so the idea that it would delay osteoporosis became the basis for a huge new marketing campaign. Slowing bone metabolism became the focus. Although estrogen was known to increase prolactin, and prolactin was known to accelerate bone loss, nearly all publications began to focus on substances in the blood or urine that corresponded to the rate of bone turnover, with the implication that increasing bone turnover would correspond to a net loss of bone.

This was the context in which, during the 1980s, articles about thyroxine's role in causing osteoporosis began to appear. The thyroid hormone supports bone renewal, and increases indicators of bone breakdown in the blood and urine. If estrogen's use was to be justified by slowing bone turnover, then the effects of thyroid, accelerating bone turnover, should be interpreted as evidence of bone destruction.

A basic problem with many of the publications on thyroid and bone loss was that they were talking about an unphysiological medical practice (prescribing the pre-hormone, thyroxine), which frequently failed to

improve thyroid function, and could even make it worse, by lowering the amount of T_3 in the tissues.

Later, it was noticed that high TSH was associated with the signs of lower bone turnover. TSH rises when there is less thyroid hormone, but (after the recombinant TSH became available for medical use) a few publications argued that it was the TSH itself, rather than the absence of thyroid hormone, that was "protecting" the bones (lowering the evidence of bone turnover). The doctrine that had been developed to support estrogen therapy was now used to oppose thyroid therapy. Keeping the TSH high would slow bone turnover.

Working in this cultural context, genetic engineers at Amgen identified a protein that inhibited the formation of osteoclast cells, and slowed bone metabolism. It was suggested that it was responsible for estrogen's suppression of the osteoclasts, and many publications appeared showing that it was increased by estrogen. It was named "osteoprotegerin," meaning "the bone protecting protein." Prolactin increases osteoprotegerin (OPG), reducing bone resorption just as estrogen does. Serotonin also increases OPG, and it turns out that OPG is elevated in all of the pathological conditions associated with high serotonin, including cancer, pulmonary artery hypertension, vascular calcification, and even bone loss.

While Arthur Everitt, Verzar, and others were studying the effects of the rat's pituitary (and other glands) on collagen, W. D. Denckla investigated the effects of reproductive hormones and pituitary removal in a wide variety of animals, including fish and mollusks. He had noticed that reproduction in various species (e.g., salmon) was quickly followed by rapid aging and death. Removing the pituitary gland (or its equivalent) and providing thyroid hormone, he found that animals lacking the pituitary lived much longer than intact animals, and maintained a high metabolic rate. Making extracts of pituitary glands, he found a fraction (closely related to prolactin and growth hormone) that suppressed tissue oxygen consumption, and accelerated the degenerative changes of aging.

Aging, estrogen, cortisol, and a variety of stresses, including radiation and lipid peroxidation, chemically alter collagen, producing cross-links that increase its rigidity, and affect the way it binds minerals. The cross-linking enzymes induced by estrogen are involved in the normal maturation of bone collagen, and at puberty when estrogen increases, bone growth is slowed, as the cross-linking and mineralization are accelerated.

With aging and the accumulation of heavy metals and polyunsaturated fats, random oxidative processes increase the cross-linking. In bones, the relatively large masses of cartilage absorb oxygen and nutrients slowly, so internally the amount of oxygen is very limited, about 1/5 as much as at the surface, and this low oxygen tension is an important factor in regulating growth, differentiation, cross-linking, and calcification, maintaining bone integrity. But in blood vessels the connective tissues are abundantly supplied with oxygen and nutrients; this is normally a factor regulating the production of collagen and its cross-linking, and preventing calcification.

When the factors promoting collagen synthesis and maturation are increased systemically, with aging and stress, the excess cross-linking slows the biological renewal process in bones, but in blood vessels the same processes creating excess cross-linking initiate a calcification process, involving the various factors that in youth are responsible for normal maturation of bone.

Prolactin, like estrogen, interferes with thyroid function and oxygen consumption.[33–35] Many years ago, repeated lactation was considered to cause osteoporosis and loss of teeth, and prolactin, which mobilizes calcium from bones for the production of milk, was recognized as an important factor in bone loss. Drugs that increase prolactin were found to cause osteoporosis. In the 40 years since the drug industry began its intense promotion of estrogen to prevent and treat osteoporosis, there has been very little attention to the fact that estrogen increases prolactin, which contributes to osteoporosis, but some people[36] have noticed that oral contraceptives and menopausal hormone treatments have damaged the bones of the inner ear, causing otosclerosis and impaired hearing, and have suggested that prolactin mediates the effect.

A few years ago, the "serotonin reuptake inhibitor" antidepressants, already known to increase prolactin by increasing the effects of serotonin, were found to be causing osteoporosis after prolonged use. Estrogen increases serotonin, which besides promoting the secretion of prolactin, also stimulates the production of parathyroid hormone and cortisol, both of which remove calcium from bone, and contribute to the calcification of blood vessels. The association between weakened bones and hardened arteries is now widely recognized, but researchers are being careful to avoid investigating any mechanisms that could affect sales of important drug products, especially estrogen and antidepressants.

Following the recognition that the SSRI drugs were causing osteoporosis, it was discovered that the serotonin produced in the intestine causes bone loss, and that inhibiting intestinal serotonin synthesis would stop bone loss and produce a bone building anabolic effect.[37] One group that had been concentrating on the interactions of genes commented that, recognizing the effects of intestinal serotonin, they had suddenly become aware of "whole organism physiology."[38]

In previous newsletters I have talked about the ability of intestinal irritation and the associated increase of serotonin to cause headaches, asthma, coughing, heart and blood vessel disease, muscular dystrophy, flu-like symptoms, arthritis, inflammation of muscles and nerves, depression, and inflammatory brain diseases. With the new recognition that serotonin is a basic cause of osteoporosis, intestinal health becomes a major issue in aging research.

The protein that inhibits intestinal formation of serotonin is the low density lipoprotein receptor-related protein. This seems likely to have something to do with the fact that "low" HDL is associated with better bones. A low level of LDL is associated with increased vertebral fractures.[39]

Cartilage synthesis and turnover are highest at night. It is inhibited by metabolic acidosis (increased lactic acid), but not by respiratory acidosis (CO_2).[40] Since most calcium is lost from bone during the night[41] in association with the nocturnal rise of the catabolic substances, such as free fatty acids, cortisol, prolactin, PTH, and adrenalin, things which minimize the nocturnal stress can decrease the bone turnover. These include calcium[42] and sugar. Catabolic substances and processes increase with aging, especially at night. Babies grow most during the night when bone turnover is high, and even a daytime nap accelerates collagen turnover.[43]

Discussions about whether a certain person's osteoporosis is "menopausal osteoporosis" or "senile osteoporosis" have neglected the possibility that osteoporosis doesn't begin in either menopause or old age, but that it is the result of life-long developmental processes that interact with all the factors that are involved in aging. The fact that the collagen content of old bone is lower than in young bone (as a percentage of bone weight) shows that the problem in osteoporosis isn't a lack of calcification, it's a deficiency of tissue renewal, parallel to sarcopenia, the decrease of muscle mass with aging. Systemically

decreased tissue renewal would account for the association of bone loss with other processes such as male baldness[44] and Alzheimer's disease.[45,46]

A high level of respiratory energy production that characterizes young life is needed for tissue renewal. The accumulation of factors that impair mitochondrial respiration leads to increasing production of stress factors, that are needed for survival when the organism isn't able to simply produce energetic new tissue as needed. Continually resorting to these substances progressively reshapes the organism, but the investment in short-term survival, without eliminating the problematic factors, tends to exacerbate the basic energy problem. This seems to be the reason that Denckla's animals, deprived of their pituitary glands, but provided with thyroid hormone, lived so long: they weren't able to mobilize the multiple defenses that reduce the mitochondria's respiratory energy production.

Several things that the geneticists would never be able to fit into their schemes of "bone regulatory molecules" such as OPG, growth hormone, parathyroid hormone, and estrogen, fit neatly with the idea that bone health is maintained by respiratory energy and tissue renewal, under the influence of thyroid hormone. For example, adrenaline, which is increased by stress, aging, and hypothyroidism (and in many cases by estrogen), causes bone loss. Even the bone loss caused by immobility can be blocked by an adrenaline blocker such as propranolol. (The stress of immobility also famously increases serotonin.) Adrenaline tends to decrease carbon dioxide and increase lactic acid, and it strongly increases parathyroid hormone (Ljunhgall S, et al., 1984).

Calcium activates mitochondrial respiration, and lowers adrenaline,[47] parathyroid hormone,[48] and prolactin.[49] Copper, which is the co-factor for the cytochrome C oxidase enzyme, activated by thyroid, is essential for bone formation and maintenance, and is consistently deficient in osteoporosis. Thyroid hormone increases the body's ability to assimilate copper.

Aspirin, which stimulates bone formation, has other thyroid-like actions, including activation of mitochondrial respiration and energy production, with an increase of cytochrome C oxidase,[50] and it lowers serotonin.[51] It also apparently protects against calcification of the soft tissues,[52] though there has been surprisingly little investigation of that. "Aspirin can promote trabecular bone remodeling, improve three-

dimensional structure of trabecular bone and increase bone density of cancellous in osteoporotic rats by stimulating bone formation. It may become a new drug for the treatment of osteoporosis".[53]

A wide range of inflammatory mediators that accelerate inflammation and bone loss also inhibit thyroid function. People who ate more polyunsaturated fat, which inhibits thyroid and oxidative metabolism, were several times more likely to have osteoporotic fractures (that is, essentially spontaneous fractures) than people who ate the least.[54]

Arachidonic acid stimulates prolactin secretion, and prolactin acts on the thyroid gland to decrease its activity, and on other tissues to increase their glycolysis (with lactate production), while decreasing oxidative metabolism.[35,55]

Living at high altitude, which strengthens bones, increases thyroid activity and decreases prolactin[56] and parathyroid hormone.[57] It lowers free fatty acids, which lower bone mass by reducing bone formation and increasing bone resorption.[58] In menopausal women, polyunsaturated fatty acids and even monounsaturated fats are associated with bone loss, fruit and vegetable consumption protects against bone loss.[59]

While it's very interesting that the drug propranol which blocks adrenaline, and drugs that block serotonin formation, have bone protective and restorative effects, they also have undesirable side effects. Food choices that optimize oxidative metabolism are the safest, as well as the most economical, way to approach the problem of osteoporosis and other degenerative changes. A person can easily perceive changes in appetite, quality of sleep, changes in skin, hair, and mood, etc., but blood tests could be used to confirm that the right choices were being made. Tests for vitamin D, parathyroid hormone, free fatty acids, and CO_2/bicarbonate, as well as the hormones, can be helpful, if a person isn't sure whether their diet, sunlight exposure, and thyroid supplementation is adequate.

The popular medical understanding of the organism is based on a mechanistic view of causality, in which genes have a central role, causing things to develop and function in certain ways, and that hormones and drugs can cause genes to increase or decrease their activity. Genes that build bones can be activated by one substance, and genes that tear down bones can be inhibited by another substance. The "osteoprotegerin" story illustrates the problem with that kind of thinking.

Vernadsky's description of an organism as a "whirlwind of atoms" is probably a better way to think of how "causality" works. The moving

air in a whirlwind forms a self-intensifying system, with the motion reducing the pressure, causing more air to be drawn into the system. The atoms moving in coordination aren't acting as separate things, but as parts in a larger thing. The way in which increased metabolism in the bones acts favorably on the metabolism of kidneys, blood vessels, lungs, liver, digestive system, etc., which in turn favors the bones' renewal, is analogous to the tendency of a whirlwind to intensify as long as there is a source of energy. The intensity of oxidative metabolism is the basic factor that permits continuing coordination of activity, and the harmonious renewal of all the components of the organism.

Osteoporosis, Harmful Calcification, and Nerve/Muscle Malfunctions

Ray Peat's Newsletter, 2006

DURING pregnancy, a woman's ability to retain dietary calcium and iron increases, and the baby seems to be susceptible to overloading. A normal baby doesn't need dietary iron for several months, as it uses the iron stored in its tissue, and recently it has been reported that normal fetuses and babies may have calcified pituitary glands. Pituitary cell death is sometimes seen with the concretions.[1] Presumably, the calcification is resorbed as the baby grows. This is reminiscent of the "age pigment" that can be found in newborns, representing fetal stress from hypoxia, since that too disappears shortly after birth. Iron overload, age pigment, and calcification of soft tissues are so commonly associated with old age, that it is important to recognize that the same cluster occurs at the other extreme of (young) age, and that respiratory limitations characterize both of these periods of life.

Calcium is probably the most popular element in physiological research, since it functions as a regulatory trigger in many cell processes, including cell stimulation and cell death. Its tendency to be deposited with iron in damaged tissue has often been mentioned. In hot weather, chickens pant to cool themselves, and this can lead to the production of thin egg shells. Carbonated water provides enough carbon dioxide to replace that lost in panting, and allows normal calcification of the shells. (Science 82, May, 1982) The deposition of calcium is the last phase of the "tertiary coat" of the egg, to which the oviduct glands successively add albumin, "egg membrane," and the shell, containing matrix proteins (including some albumin[2]) and calcium crystals. Albumin is the best understood of these layers, but it is still complex and mysterious; its unusual affinity for metal ions has invited comparisons with proteins of the immune system. It is known to be able to bind iron strongly, and this is considered to have an "immunological" function, preventing the invasion of organisms that depend on iron. Maria de Sousa[3] has argued that the oxygen delivery system and the immune system evolved together, recycling iron in a tightly controlled system.

The role of macrophages in the massive turnover of hemoglobin, and as osteoclasts, gives us a perspective in which iron and calcium are

handled in analogous ways. Mechnikov's view of the immune system, growing from his observations of the "phagocytes," similarly gave it a central role in the organism as a form-giving/nutrition-related process. In a family with "marble-bone disease," or osteopetrosis, it was found that their red blood cells lacked one form of the carbonic anhydrase enzyme, and that as a result, their body fluids retained abnormally high concentrations of carbon dioxide. Until these people were studied, it had been assumed that an excess of carbon dioxide would have the opposite effect, dissolving bones and causing osteoporosis or osteopenia, instead of osteopetrosis. The thyroid hormone is responsible for the carbon dioxide produced in respiration. Chronic hypothyroidism causes osteopenia, and in this connection, it is significant that women (as a result of estrogen's effects on the thyroid) are much more likely than men to be hypothyroid, and that, relative to men, women in general are "osteopenic," that is, they have more delicate skeletons than men do.

In an experiment, rats were given a standard diet, to which had been added 1 % Armour thyroid, that is, they were made extremely hyperthyroid. Since their diet was inadequate (later experiments showed that this amount of thyroid didn't cause growth retardation when liver was added to the diet) for their high metabolic rate, they died prematurely, in an apparently undernourished state, weighing much less than normal rats. Their bones, however, were larger and heavier than the bones of normal rats. A few incompetent medical "studies" have made people fear that "taking thyroid can cause osteoporosis." Recognizing that hypothyroid women are likely to have small bones and excessive cortisol production, the inadequate treatment of hypothyroidism with thyroxin (the thyroid-suppressive precursor material), is likely to be associated with relative osteoporosis, simply because it doesn't correct hypothyroidism. Similar misinterpretations have led people to see an association between "thyroid use" (generally thyroxin) and breast cancer—hypothyroid women are likely to have cancer, osteoporosis, obesity, etc., and are also likely to have been inadequately treated for hypothyroidism. T_3, the active form of thyroid hormone, does contribute to bone formation.[4]

Around the same time (early 1940s) that the effects of thyroid on bone development were being demonstrated, progesterone was found to prevent age-related changes in bones, and "excessive" seeming doses of thyroid were found to prevent age-related joint diseases in rats.

A logical course of events, building on these and subsequent discoveries, would have been to observe that the glucocorticoids cause a negative calcium balance, leading to osteoporosis, and that thyroid and progesterone oppose those hormones, protecting against osteoporosis. But the drug industry had discovered the profits in estrogen ("the female hormone") and the cortisone-class of drugs. Estrogen was promoted to prevent miscarriages, to stop girls (and boys) from growing too tall, to cure prostate and breast cancer, to remedy baldness, and 200 other absurdities. As all of those frauds gradually became untenable, even in the commercial medical culture, the estrogen industry began to concentrate on osteoporosis and femininity. Heart disease and Alzheimer's disease back those up.

"If estrogen causes arthritis, prescribe prednisone for the inflammation. If prednisone causes osteoporosis, increase the dose of estrogen to retard the bone-loss. People are tough, and physiological therapies aren't very profitable."

Fifteen years ago I noted in a newsletter that hip fractures most often occur in frail, underweight old women, and that heavier, more robust women seem to be able to bear more weight with less risk of fracture. Although I hadn't read it at the time, a 1980 article[5] compared patients with a broken hip or arm with a control group made up of hospitalized orthopedic patients with problems other than hip or arm fractures. The fracture cases' weight averaged 19 pounds lighter than that of the other patients. They were more than 3.6 times as likely to be alcoholic or epileptic. It would be fair to describe them as a less robust group.

Since the use of estrogen has become so common in the U.S., it is reasonable to ask whether the incidence of hip fractures in women over 70 has declined in recent decades. If estrogen protects against hip fractures, then we should see a large decrease in their incidence in the relevant population.

Hip fractures, like cancer, strokes, and heart disease, are strongly associated with old age. Because of the baby-boom, 1945 to 1960, our population has a bulge, a disproportion in people between the ages of 35 and 50, and those older. Increasingly, we will be exposed to publicity about the declining incidence of disease, fraudulently derived from the actually declining proportion of old people. For example, analyzing claims based on the pretense that the population bulge doesn't exist,

I have seen great publicity given to studies that would imply that our life-expectancy is now 100 years, or more.

Comparing the number of hip fractures, per 1000 75 year old women, in 1996, with the rate in 1950, we would have a basis for judging whether estrogen is having the effect claimed for it.

The x-ray data seem to convince many people estrogen is improving bone health, by comparing measurements in the same person before and after treatment. Does estrogen cause water retention? Yes. Does tissue water content increase measured bone density? Yes. Are patients informed that their "bone scans" don't have a scientific basis? No. The calcification of soft tissues under the influence of estrogen must also be taken into account in interpreting x-ray evidence.[6] Granted that woman who are overweight have fewer hip fractures (and more cancer and diabetes), what factors are involved? Insulin is the main factor promoting fat storage, and it is anabolic for bone. (Rude and Singer, "Hormonal modifiers of mineral metabolism.") The greatest decrease in bone mass resulting from insulin deficiency was seen in white females, and after five years of insulin treatment, there was a lower incidence of decreased bone mass.[7] McNair, et al.,[8,9] found that the loss of bone mass coincided with the onset of clinical diabetes. Since excess cortisol can cause both high blood sugar and bone loss, when diabetes is defined on the basis of high blood sugar, it will often involve high blood sugar caused by excess cortisol, and there will be calcium loss. Elsewhere, I have pointed out some of the similarities between menopause and Cushing's syndrome; a deficiency of thyroid and progesterone can account for many of these changes. Nencioni and Polvani have observed the onset of progesterone deficiency coinciding with bone loss, and have emphasized the importance of progesterone's antagonism to cortisol.

Johnston[10] found that progesterone (but not estrone, estradiol, testosterone, or androstenedione) was significantly lower in those losing bone mass most rapidly.

Around the age of 50, when bone loss is increasing, progesterone and thyroid are likely to be deficient, and cortisol and prolactin are likely to be increased. Prolactin contributes directly to bone loss, and is likely to be one of the factors that contributes to decreased progesterone production.

Estrogen tends to cause increased secretion of prolactin and the glucocorticoids, which cause bone loss, but it also promotes insulin

secretion, which tends to prevent bone loss. All of these factors are associated with increased cancer risk.

Thyroid and progesterone, unlike estrogen, stimulate bone-building, and are associated with a decreased risk of cancer. It seems sensible to use thyroid and progesterone for their general anti-degenerative effects, protecting the bones, joints, brain, immune system, heart, blood vessels, breasts, etc.

But the issue of calcification/decalcification is so general, we mustn't lose interest just because the practical problem of osteoporosis is approaching solution.

For example, healthy high energy metabolism requires the exclusion of most calcium from cells, and when calcium enters the stimulated or deenergized cell, it is likely to trigger a series of reactions that lower energy production, interfering with oxidative metabolism. During aging, both calcium and iron tend to accumulate and they both seem to have an affinity for similar locations, and they both tend to displace copper. (Compare K. Sato, et al., on the calcification of copper-containing paints.) Elastin is a protein, the units of which are probably bound together by copper atoms. In old age, elastin is one of the first substances to calcify, for example in the elastic layers of arteries, causing them to lose elasticity, and to harden into almost bone-like tubes. In the heart and kidneys, the mitochondria (rich in copper-enzymes) are often the location showing the earliest calcification, for example when magnesium is deficient.

Obviously, certain proteins have higher than average affinity for copper, iron, and calcium. For example, egg-white's unusual behavior with copper can be seen if you make a meringue in a copper pan—the froth is unusually firm. My guess is that copper atoms bind the protein molecules into relatively elastic systems. In many systems, calcium forms the link between adhesive proteins.

In brain degeneration, the regions that sometimes accumulate aluminum, will accumulate other metals instead, if they predominate in the environment; calcium is found in this part of the brain in some of the Pacific regions studied by Gajdusek. Certain cells in the brain used to be called "metalophils," because they could be stained intensely with silver and other metals; I suppose these are part of the immune system, handling iron as described by Maria de Sousa. Macrophages have been proposed as an important factor in producing atherosclerotic plaques.[11] There is evidence that they (and not smooth muscle cells) are the char-

acteristic foam cells, and their conversion of polyunsaturated oils into age pigment accounts for the depletion of those fats in the plaques. The same evidence could be interpreted as a defensive reaction, binding iron and destroying unsaturated fatty acids, and by this detoxifying action, possibly protecting against calcification and destruction of elastin.[12]

Since carbon dioxide and bicarbonate are formed in the mitochondria, it is reasonable to suppose that the steady outward flow of the bicarbonate anion would facilitate the elimination of calcium from the mitochondria. Since damaged mitochondria are known to start the process of pathological calcification in the heart and kidneys, it probably occurs in other tissues that are respiratorily stressed. And if healthy respiration, producing carbon dioxide, is needed to keep calcium outside the cell, an efficient defense system could also facilitate the deposition of calcium in suitable places—depending on specific protein binding. The over-grown bones in the hyperthyroid rats and the women with osteopetrosis suggest that an abundance of carbon dioxide facilitates bone formation. Since no ordinary inorganic process of precipitation/crystallization has been identified that could account for this, we should consider the possibility that the protein matrix is regulated in a way that promotes (or resists) calcification. The affinity of carbon dioxide for the amine groups on proteins (as in the formation of carbamino hemoglobin, which changes the shape of the protein) could change the affinity of collagen or other proteins for calcium. Normally, ATP is considered to be the most important substance governing such changes of protein conformation or binding properties, but ordinarily, ATP and CO_2 are closely associated, because both are produced in respiration. Gilbert Ling has suggested that hormones such as progesterone also act as cardinal adsorbants, regulating the affinity of proteins for salts and other molecules.

Cells have many proteins with variable affinity for calcium; for example in muscle, a system called the endoplasmic reticulum, releases and then sequesters calcium to control contraction and relaxation. (This calcium-binding system is backed up by—and is spatially in close association with—that of the mitochondrion.) Ion-exchange resins can be chemically modified to change their affinity for specific ions, and molecules capable of reacting strongly with proteins can change the affinities of the proteins for minerals. What evidence is there that carbon dioxide could influence calcium binding? The earliest deposition of

crystals on implanted material is calcium carbonate.[13] In newly formed bone, the phosphate content is low, and increases with maturity. While mature bone has an apatite-like ratio of calcium and phosphate, newly calcified bone is very deficient in phosphate (according to Dallemagne, the initial calcium to phosphorus ratio is 1.29, and it increases to 2.20.)[14]

The carbonate content of bone is often ignored, but in newly formed bone, it is probably the pioneer. Normally, "nucleation" of crystals is thought of as a physical event in a supersaturated solution, but the chemical interaction between carbon dioxide and amino groups (amino acids, protein, or ammonia, for example) removes the carbon dioxide from solution, and the carbamino acid formed becomes a bound anion with which calcium can form a salt. With normal physiological buffering, the divalent calcium (Ca_2^+) should form a link between the monovalent carbamino acid and another anion. Linking with carbonate (CO_{32}^-), one valence would be free to continue the salt-chain. This sort of chemistry is compatible with the known conditions of bone formation.

Klein, et al.,[15] think of uncoupled oxidative phosphorylation in terms of "subtle thermogenesis," which isn't demonstrated in their experiment, but their experiment actually suggests that stimulated production of carbon dioxide is the factor that stimulates calcification. Their experiment seems to be the *in vitro* equivalent of the various observations mentioned above. DHEA, which powerfully stimulates bone formation, is (like thyroid and progesterone) thermogenic, but in these cases, the relevant event is probably the stimulation of respiration, not the heat production. In pigs (Landrace strain) susceptible to malignant hyperthermia, there is slow removal of calcium from the contractile apparatus of their muscles. Recent evidence shows that an extramitochondrial NADH-oxidase is functioning. This indicates that carbon dioxide production is limited. I think this is responsible for the cells' sluggishness in expelling calcium.

Stress-susceptible pigs show abnormalities of muscle metabolism (e.g., high lactate formation) that are consistent with hypothyroidism.[16,17]

Malignant hyperthermia during surgery is usually blamed on genetic susceptibility and sensitivity to anesthetics.[18,19] Hypertonicity of muscles, various degrees of myopathy and rigidity, and uncoupling of oxidative phosphorylation occur in these people, as in pigs. Lactic acidosis suggests that mitochondrial respiration is defective in the people, as in the pigs. Besides the sensitivity to anesthetics, the muscles of these

people are abnormally sensitive to caffeine and elevated extracellular potassium. During surgery, artificial ventilation, combined with stress, toxic anesthetics, and any extramitochondrial oxidation that might be occurring (such as NADH-oxidase, which produces no CO_2), make relative hyperventilation a plausible explanation for the development of hyperthermia. Hyperventilation can cause muscle contraction. Panting causes a tendency for fingers and toes to cramp. Free intracellular calcium is the trigger for muscle contraction (and magnesium is an important factor in relaxation.) Capillary tone, similarly, is increased by hyperventilation, and relaxed by carbon dioxide. The muscle-relaxing effect of carbon dioxide shows that the binding of intracellular calcium is promoted by carbon dioxide, as well as by ATP. The binding of calcium in a way that makes it unable to interfere with cellular metabolism is, in a sense, a variant of simple extrusion of calcium, and the binding of calcium to extracellular materials. A relaxed muscle and a strong bone are characterized by bound calcium.

Activation of the sympathetic nervous system promotes hyperventilation. This means that hypothyroidism, with high adrenalin (resulting from a tendency toward hypoglycemia because of inefficient use of glucose and oxygen), predisposes to hyperventilation.

Muscle stiffness, muscle soreness and weakness, and osteoporosis all seem to be consequences of inadequate respiration, allowing lactic acid to be produced instead of carbon dioxide. Insomnia, hyperactivity, anxiety, and many chronic brain conditions also show evidence of defective respiration, for example, either slow consumption of glucose or the formation of lactic acid, both of which are common consequences of low thyroid function. Several studies[20] suggest that abnormal calcium regulation is involved in epilepsy.

The combination of supplements of thyroid (emphasizing T_3), magnesium, progesterone and pregnenolone can usually restore normal respiration, and it seems clear that this should normalize calcium metabolism, decreasing the calcification of soft tissues, increasing the calcification of bones, and improving the efficiency of muscles and nerves. (Magnesium, like carbonate, is a component of newly formed bone.) The avoidance of polyunsaturated vegetable oils is important for protecting respiration; some of the prostaglandins they produce have been implicated in osteoporosis, but more generally, they antagonize thyroid function and they can interfere with calcium control. The pres-

ence of the "Mead acid" (the omega-9 unsaturated fat our enzymes synthesize) in cartilage suggests a new line of investigation regarding the bone-toxicity of the polyunsaturated dietary oils.

Pathological Science & General Electric

Threatening the Paradigm

Ray Peat's Newsletter, 2012

EVERYTHING in biology depends on the internal order of cells, and on the interactions of each cell with its surroundings. All of these orderly interactions involve contacts between biological molecules and water. The forces regulating interactions on that scale must be understood before life can be understood, but the nature of the forces at these interfaces has been controversial for 100 years.

In 1953, physicist Irving Langmuir gave a talk at the General Electric laboratory about what he called "pathological science." That talk is still resonating in the scientific culture, and it is used to reinforce attitudes similar to those held by Langmuir, i.e., the dominant scientific paradigm of the 20th century, and to justify certain institutions that regulate innovation.

For Langmuir, there was a clearly defined "scientific method," and he said some people were led away from the proper method by wishful thinking to interpret ambiguous results as confirmations of their hypothesis. He listed 6 symptoms of pathological science: 1) An effect produced by a barely detectable cause, and 2) the effect is barely detectable, or many measurements are needed because of the very low statistical significance of the results, 3) claims of great accuracy, 4) they involve fantastic theories contrary to experience, 5) criticisms are met by *ad hoc* excuses, and 6) the ratio of supporters to critics approaches 50 %, then fades toward zero. He failed to mention these features in any research that supported his view of things, and called an idea pathological when people continued to work on it despite disapproval by the recognized experts. He didn't mention the Nobel Prizes that were given for the worm theory of cancer or for treating psychological problems with lobotomies, and he didn't mention that there were organized campaigns against the publication of disapproved ideas.

The dominant view in biology, which is analogous to Langmuir's view in physics, is that all decisive cellular processes involve the direct mechanical contact of one molecule with another, the activation of a lock (an enzyme or receptor) by a key that has the right shape, or the adhesion of a molecule to another substance according to its chemical composition.

An alternative view, now clearly supported by the evidence, is that there are forces that aren't merely between molecular surfaces, but rather that the local conditions at the surfaces of proteins and other molecules, and the properties of the solvent water, are modified by the surrounding conditions. It is this alternative view that is now making progress in understanding disease and health, regeneration and degeneration. But to judge the new work, it's important to know the nature of the opposition.

Thomas Edison, who was adept at publicizing himself as the inventor of ideas he had bought or stolen, founded General Electric. Attempting to eliminate Nikola Tesla's system of alternating current, since Edison was invested in direct current systems, Edison's GE tried to convince the public that direct current was safer, by using alternating current to electrocute an elephant, and by promoting its use in the electric chair. GE eventually gave up the direct current technology for electrifying cities, and they refined the electric light bulb and were fairly successful in controlling, practically monopolizing, that market, and in shortening the life of incandescent bulbs. Carbon filament bulbs made around 1900 often lasted decades; I had one that kept working until it was broken during a move in 1960. Light bulbs made in England 65 years ago, and in the Soviet Union, and bulbs currently made in China, had a life expectancy five times as long as the bulbs made in the U.S. since GE learned how to carefully control the rate at which the tungsten filament deteriorates.

Irving Langmuir was their leading light bulb scientist. In his 1932 Nobel lecture, he tediously argued that molecules of gas can form only one layer on a surface such as a filament. About 17 years earlier, Michael Polanyi had demonstrated that molecules can be adsorbed in multilayers, but his evidence was dismissed because, according to the understanding of industrial experts such as Langmuir, and the leading scientific authorities, Einstein, Nernst, and Haber, it was impossible. They were committed to an explanatory system that didn't allow events such as those Polanyi described.

Although Polanyi knew that his adsorption isotherm was more realistic than Langmuir's (he had demonstrated many cases that Langmuir's didn't describe correctly), and also easier to understand, he taught Langmuir's isotherm to his students, because he knew that they would be required to know it to pass their examinations. He knew he had risked

his career by his earlier exposition of his ideas, and he was unwilling to endanger his students' careers by involving them in the controversy.

From 1920 to 1926, before the advent in 1927 of "quantum physics" (with its still-argued features of delocalized electrons, molecular orbitals, resonance, non-locality, incommensurability, indeterminism), Polanyi had turned his attention from the physics of adsorption to chemical structure, and his group was the first to show that cellulose was made up of long molecules, polymers, rather than of just associated clusters. That idea didn't catch on, so he turned to the behavior of crystals and metals. He found that crystals were much weaker than they should be, according to the strength of the bonds between their atoms, and showed that this was because of defects, and that during repeated stresses, they became weaker, as energy migrated through relatively long distances in the substance, to concentrate the defects. The idea of lattice defects was acceptable at that time, but long-range mobility of bond energy was no more acceptable then than it had been when J.C. Bose described metal fatigue, decades earlier.

Polanyi also showed that the strength and rigidity of a crystal were altered when the crystal was immersed in water. Again, such an influence of a surface on the over-all physical properties of a solid substance had no noticeable effect on the scientific culture, although his results were published in the major journals. To adjust one's interpretive system at that time to rationalize Polanyi's results would have required discarding the basic assumptions that were behind Einstein's explanation of the photoelectric effect, and maybe even his theory of Brownian motion. However, by 2011, fewer people have invested their personal development in those ideas of short-range electrical binding forces that prevailed early in the 20th century, and now, for example, the evidence of "delocalized holes in DNA" can be discussed more openly. Eventually, science textbooks may be rewritten to show a steady progression of understanding from Bose, though Polanyi, Perutz, Szent-Györgyi, Ling, and Damadian (inventor of the MRI, holder of the patents infringed by GE, non-winner of the Nobel prize).

In 1933 J.D. Bernal had proposed a structural model of water that contained a considerable amount of order[1] but by the 1950s the idea of spontaneous ordering in water was out of style, and he worked out a more random structure. Max Perutz, continuing the study of hemoglobin he had begun with Bernal, became concerned with long range forces acting

through water: "The nature of the forces which keep particles parallel and equidistant across such great thicknesses of water is not yet clear." Normal wet crystals of methemoglobin contain regular layers of water 15 Å thick. He suggested that a laminated structure of the water could plausibly explain his measurements. Comparing the protein crystal to montmorillonite particles, which incorporate several layers of water, each 3 Angstroms thick, each layer of water in the protein crystal would be 4 Angstroms thick, since swelling proceeds in discrete steps of that thickness. 52.4 % of the volume of Perutz's normal, stable, wet protein crystals consisted of liquid. Part of the water is a fixed monolayer, but the rest is apparently in the form of mobile, interactive, multilayers. By 1952, Perutz had decided that long range forces weren't involved in hemoglobin crystallization, but he didn't comment on the long range ordering of clays, tobacco mosaic viruses, and other particles and gels. In 2005, an interlaminar distance of 17.9 Å, or six layers of water, still seems to be stable in hydrated montmorillonite.[2] Clay continues to be studied in relation to nuclear waste disposal, so the effects of surfaces on water's properties haven't been entirely excluded from science. The interfacial water in clay has special catalytic properties that make it interesting to many researchers.[3]

Bernal's and Perutz' conformity in the 1950s rejection of long range forces and an ordered structure of water represented the dominant ideas in physics and physical chemistry, but many people (with very little financial or institutional support) were continuing to study the structure of water, both in the bulk phase and near surfaces, as in cells. Philippa Wiggins, Albert Szent-Györgyi, Carlton Hazlewood, Freeman Cope, and Ray Damadian were among the most active proponents of the importance of structured water in living cells. Walter Drost-Hansen showed that water near surfaces (vicinal water) is several percent less dense, and has a greater heat capacity, than bulk water, and that bulk water undergoes transitions at certain temperatures that alter its effects on enzyme reactions.

The question regarding the nature of the forces at surfaces or interfaces affects how we think about everything, from life to nuclear energy. The political and economic implications of "non-local energy" (which is most obvious at surfaces) have at times led to organized campaigns to discourage research in those areas. When Alexandre Rothen found (beginning in 1946) that enzymes and antibodies had non-local effects,

several prestigious publications claimed to show how he must have been mistaken: The films he used must have been porous, despite his demonstrations of their continuity.

The methods he developed at Rockefeller Institute quickly became standard for accurately measuring very thin films. In the early 1970s, a GE employee, Ivar Giaever, visited Rothen's lab to learn his methods. Shortly after his visit, he demonstrated his "new method" to the press. I saw an article about it in *Science News*, and wrote them a short letter, pointing out that the method had been developed and used by Rothen much earlier; they printed my note, which could be seen as a criticism of the author of the news article. About a week later, I got a letter from Rothen, thanking me for writing to the magazine; he said they had refused to publish his own letter explaining the situation, including his interactions with Giaever during the visit. I assume that the magazine felt some kind of pressure to protect Giaever and GE from an authoritative accusation of scientific dishonesty.

In 1968 when I began studying biology at the University of Oregon, the professor of microscopy, Andrew Bajer, posted a display of dozens of micrographs, with explanatory captions, along the halls near the entrance of one of the science buildings. The one that interested me most showed orderly rows of regularly formed objects on a smooth surface. The caption described it as clusters of sodium atoms, deposited from vapor, on a film of a polymer (formvar, I think), under which was a quartz crystal. The caption noted that the sodium atoms had condensed in a pattern representing the crystal structure of the underlying quartz. Although Rothen's work involved proteins deposited from solution, rather than sodium atoms deposited from vapor, Bajer's image illustrated visually the projection of the forces of crystal structure through an amorphous film. This seemed to be a graphic representation of Polanyi's adsorption potential, a force acting on atoms in the space near a surface, as opposed to Langmuir's local atomic force that didn't reach beyond the first layer of atoms. The long range order in this case arranged atoms geometrically, while Rothen's preparations showed a "projected" specificity, but of a more complex sort.

Just a few months later, someone who knew of Stephen Carter's demonstration that fibroblasts will migrate on a glass slide coated with a gold film, toward areas of greater thickness of the metal, did a similar experiment, but with a formvar film between the gold and the cells. The

cells still migrated up the gradient, toward the area of thicker gold under the film. The reaction to that publication was the same as the reaction to Rothen's work 20 years before, the formvar films contained holes, and the cells were reaching through the film to touch the metal surface, sort of like kids peeking around a blindfold when they aren't supposed to be watching. I didn't understand how the holes would explain anything, even if there were holes and if the cells had put out many long filopodia to reach through the film, but in fact making a formvar film is a very standardized technique. They can be made "holey," or like a very open net, or they can be made solid, just by choosing the concentration of the polymer used. The difference is very clear, under an electron microscope, but the professors needed an excuse for dismissing something they didn't want to understand. Further work was discouraged by their ridicule.

In Russia, GE had very little influence on the acceptability of ideas in science, and Boris Deryagin continued (from the 1930s until 1990) to study the properties of water near surfaces. In 1987 his group demonstrated that cells can clear particles from a space around themselves, extending more than a cell's diameter away. This distance is similar to the cell free zone in flowing blood adjacent to the walls of arterioles, which is probably the result of multiple interacting forces. At present, processes such as cell adhesion of leukocytes and stem cells (and tumor cells) to the blood vessel wall and movement through the blood vessel into the tissues (diapedesis) is explained in terms of adhesion molecules, disregarding the plausible effects of long range attractive or repulsive forces. Clumping or sludging of red blood cells occurs when the organism is failing to adapt to stress, and could be reasonably explained by a failure of protective repulsive fields. These fields are developed and maintained by metabolism, primarily oxidative energy metabolism, and are modified by endogenous regulatory substances and external conditions, including electromagnetic and electrical fields.

100 years ago, Albert Einstein was a major influence in popularizing the "only local" dogma of atomic interactions. (His work led directly to "quantum physics," but he never accepted its irrational implications.[†] I don't think he ever considered that the assumptions in his [atomic-quantized] theory of the photoelectric effect were the problem.) One charged atom is completely neutralized by its association with an oppositely charged atom, and the force is described by the inverse square law, that the force decreases with the square of the distance between point

charges, meaning that the force is very strong at very small distances. However, a physical surface, a plane where one substance ends and another begins, follows different rules.

Different substances have different electron affinities, creating a phase boundary potential, a charged layer at the interface. (Electrical double layers at interfaces are important in semiconductors and electrodes, but biologists have carefully avoided discussing them, except in the very narrow context of electrodes.) The electrically active surface of a substance, even though it's made of atoms and electrons, projects its electrical field in proportion to its area. This principle is as old as Coulomb's law, but the habit of thinking of electrical charge on the atomic scale seems to make people forget it. It's exactly the sort of space-filling field that Polanyi's adsorption isotherm describes. It's also involved in crystal strength and elasticity as studied by Polanyi, in piezoelectricity, and in generation of semiconduction in amorphous materials, as used in Stan Ovshinsky's processes.

Long range structural and electronic interactions produce "antenna" effects, which are sensitive to very weak fields, whether they originate inside or outside of the organism. Magnetobiology is often treated as a pseudo-science or pathological science, because "real science" considers heating and chemical bond reactions to be the only possible effects of low energy fields or radiation. Solco Tromp, beginning in the 1930s, showed that cells behave like liquid crystals, and that liquid crystals can respond to very low electrical and magnetic fields.

If the adsorption potential structures the water in its region of space, this interfacial water is now a new phase, with different physical properties, including new catalytic properties, such as those recognized by the clay investigators (which increased its ability to dissolve the clay minerals).

Several versions of Langmuir's Pathological Science talk have been published, some of them adding new examples, including "polywater." Langmuir died in 1957, and the first example of polywater was observed by N.N. Fedyakin was observed in 1961. When finely drawn quartz or

† From Einstein's 1926 letter to Max Born: "Quantum mechanics is very worthy of regard. But an inner voice tells me that this is not yet the right track. The theory yields much, but it hardly brings us closer to the Old One's secrets. I, in any case, am convinced that He does not play dice." Quoted in P. Busch and G. Jaeger, "Unsharp quantum reality," 4 May 2010.

Pyrex glass capillary tubes (with inside diameter of up to a tenth of a millimeter) are suspended in a container with the air pressure reduced, above a container of distilled water, so that they are exposed to pure water vapor at room temperature, after a period of an hour or more (sometimes days or weeks were required) a small drop of liquid condenses inside some (a small percentage) of the capillary tubes. Above some of the original drops, a second drop sometimes appeared, that would enlarge as the first drop shrank. This separation of water into two fractions was itself anomalous, and the upper drop was found to be denser than normal water. Many people began studying its properties. Fedyakin found that its thermal expansion was greater, and its vapor pressure lower, than ordinary water. Others found that it had a higher refractive index, viscosity, and surface tension, as well as greater density, than ordinary water. Birefringence (the splitting of a beam of light into two rays when it passes through an ordered material) was observed in the anomalous water, and this usually indicates the presence of a polymer[4–6] or crystallinity. The water associated with clay is also birefringent,[7] and its properties are different when the clay absorbs it from the vapor phase or from liquid water.

Hysteresis is a lag in the behavior of a system, resulting when the internal state of the system is altered by an action, so that it responds differently to a repetition of that action; it's the memory of a system that exists only when the system has internal structure. For example, a gas has relatively little hysteresis. Perfect elasticity is one extreme of an ordered solid, but most solids have some hysteresis, in which the deformed material fails to spring back immediately. Hysteresis of adsorption can be seen at the edges of a drop of water on a tilted surface, with a steeper contact angle on the newer contact at the lower edge, showing a reluctance of the water to wet a new surface, a lower contact angle where the drop is pulling away from the upper surface, a reluctance to break the contact. The same is seen at the edges of an evaporating-shrinking drop, or a growing drop. Everyone perceives this memory function of water.

Boris Deryagin studied both the elasticity and the hysteresis of water near surfaces, and both approaches showed that it contained internal structure. Many dogmatic professors denied that water could show elasticity or "memory," because of their interpretive system/mental rigidity.

When Fedyakin got the help of Deryagin's lab in analyzing the anomalous material, many different methods of purifying the glass and the water and the vessel were tried, and its properties were analyzed in many different ways. When Deryagin first described the material at a conference in Europe, there was great interest, and eventually hundreds of people began investigating it.

A British laboratory was the first to get a sample of Deryagin's material in 1966, and their tests confirmed Deryagin's.

The US Bureau of Standards, having the best analytical instruments in the world (including a microscope spectrometer), studied it carefully. They[6] found that its bonds were stronger than those in ordinary water, and they compared its absorption spectrum (by computer) with those of 100,000 known substances, and found that it corresponded with nothing previously known. It didn't have the absorption band of normal water. When it evaporated, it left no visible residue, and it turned into ordinary water when heated. They concluded that the physical structure that would best fit its absorption spectrum was a polymerized form of water, so they called it "polywater." Later, Lippincott and others[8,9] did proton magnetic resonance analyses that showed a difference of polywater from normal water in the hydrogen bonding, a "deshielding" of the protons, meaning that the electrons were arranged differently in the molecules.

In 1969 there were many threats to the dominant paradigm, and many people were demanding a change in the government's funding priorities. The public excitement about polywater following the many confirmations of its existence was disturbing to the defenders of the paradigm. Philip Abelson, the chief editor of Science magazine, used the magazine to further his political beliefs.

Denis Rousseau, a young researcher at Bell Labs (who now writes about pathological science), published a series of articles in Science describing his tests of polywater. He played tennis until his tee-shirt was soaked with sweat, then extracted and concentrated the sweat into a small gummy pellet. He reported that the infrared spectrum of the sweat concentrate (largely sodium lactate) was very similar to that of polywater. One of the techniques he used to identify impurities (electron spectroscopy) requires a high vacuum, so there couldn't be any normal water present. The water associated with ionic impurities is driven off at low temperatures compared to the temperature needed to decompose the anomalous water.

Although Rousseau's "explanation" was ludicrous, it was just the thing the professors needed to prevent further challenges to their paradigm. Although Deryagin published more evidence of the purity of the anomalous water in 1972, by 1973 the mass media, including Science magazine, were saying that polywater didn't exist, and that Deryagin had admitted that he was mistaken. But polywater was Lippincott's term, and what Deryagin said was that silica was the only impurity that could be identified in the anomalous material.

There are many antecedents to anomalous water in the literature. In the 1920s, W.A. Patrick of Johns Hopkins and J. L. Shereshefsky at Howard university investigated the properties of water in fine capillary tubes and found that the vapor pressure wasn't the same as that of normal water. (This is what would have been expected, if Polanyi's adsorption isotherm had been accepted.) The density of water in clay has been found to be slightly less than normal. This water bound to clay requires a high temperature to eliminate, similar to the decomposition temperature of polywater. The catalytic properties of interfacial water in clay are recognized, causing it to solublize components of the clay. So it's hard to imagine that there wouldn't be some silica in the material formed in quartz or glass capillary tubes.

The only thing pathological about the polywater episode was the extreme effort that was made to stigmatize a whole category of research, to restore faith in the old doctrine that insisted there are no long range ordering processes anywhere in the universe. The successful campaign against polywater strengthened the mainstream denial of the evidence of ordering in interfacial and intracellular water, kept the doctrine of the lipid bilayer cell membrane alive, and up until the present has prevented the proper use of MRI scans in medical diagnosis.

In 1946, while the government was studying the way nuclear fallout was influenced by the weather, a group at GE, led by Langmuir, began experimenting with weather control by means of "cloud seeding." Langmuir observed that the energy in a cloud system was greater than that in an atomic bomb, and that by seeding clouds in Europe, disastrous weather effects could be created in the Soviet Union. The GE group convinced the Pentagon to become involved in weather control. (The physicist Ross Gunn was transferred directly from work on the atomic bomb to direct the cloud seeding project.) In one of Langmuir's seeding experiments, he claimed that he had changed the direction of a hurricane

moving toward the U.S. When a young researcher pointed out that the weather service had predicted exactly that change of direction, based on the temperatures of ocean currents, Langmuir became angry, and told the man that he wasn't going to explain it to him, because he was too stupid to understand.

Langmuir's attitude toward science was exactly what GE wanted; his career and reputation were part of the corporation's public relations and business plan. Science was whatever GE thought was good for their business. That science was pathological, sometimes by Langmuir's own defining features, most of the time by the effects it has had on society. The Manhattan Project was central to GE's business plan, and when the bomb project was completed GE and the Atomic Energy Commission found that the same subsidies could be used to develop nuclear generators of electricity. Following Edison's pioneering work with x-rays, x-ray imaging machines had become very profitable for GE. It was important to assure the public that medical, industrial, and military radiation was well understood, well controlled, safe, and essential for the general welfare. In their view, if every woman could have access to GE's x-ray mammograms, for example, almost all breast cancers could be cured. The radiation exposure from living near a GE nuclear power generator is infinitesimal compared to living in Denver or flying in an airplane. (There is some discussion of these issues in my January, 2011 newsletter, "Radiation and growth.") Public relations involves everything from "basic research" to television advertising.

If nuclear energy is as safe as the industry and governments say it is, the reactors should be located in the centers of large cities, because transmitting electric power long distances is presently wasting 50 % of the power.[10] Admiral Rickover, influential advocate of nuclear power, said "…every time you produce radiation, [a] horrible force [is unleashed,] and I think there the human race is going to wreck itself. [We must] outlaw nuclear reactors." (January, 1982 congressional testimony). Helen Caldicott says Fukushima is many times worse than Chernobyl. The radioactive cesium in German mushrooms and truffles hasn't decreased 25 years after Chernobyl, and the German government is spending increasing amounts to compensate hunters for the wild boars (who eat truffles) that must be disposed of as radioactive waste.

General Electric sent its condolences to the people of Japan, and said the reactors of that design had functioned well for 40 years; they didn't

mention that Unit I at Fukushima had been scheduled to be shut down on March 26, 2011, the end of its 40 year life expectancy. In late March, as the accident continued, Tepco applied for a permit to build two new reactors at the Fukushima site. In the U.S., the government continues its loan guarantee policy to subsidize new reactor construction.[†]

After many years of working with his metalized slides, Alexandre Rothen found that their activity, the strength of their long-range influence, varied with a 24 h cycle, and that their activity could also be destroyed or restored by putting them in a magnetic field, parallel or perpendicular to the surface. Around the same time, a Russian biochemist, Simon Shnoll, noticed that there were cyclic changes in well defined enzymic reactions. Like Rothen, Shnoll did experiments that showed that the earth's motion (relative to the stars) affected measurements in the laboratory, even measurements of alpha particles produced by nuclear fission. Organized matter, whether it's cellular or in the crystalline solid state, is susceptible to surrounding conditions.

In 1971 or '72 I learned of H.C. Dudley's idea of a "neutrino sea," that he suggested might be equivalent to the "luminiferous ether" that had previously been used to explain light and electromagnetism. I wrote to him, asking if he thought neutrinos could be involved in biological ordering processes by resonating with matter under some circumstances. He had been developing a theory, in which atomic nuclei might interact with a neutrino "ether," in ways that could affect the decay rate of the unstable isotopes, and so it didn't seem unreasonable to him that biological structures might also interact with neutrinos. In October, 1972, he published a purely theoretical article in which he explained that nuclear reactors might under some conditions become dangerously unstable. I had earlier seen a newspaper article about an experiment by a physicist, J.L. Anderson, in which radioactive carbon-14 didn't follow the normal rules of random decay, when the isotope was incorporated into an oil, which was spread in a monolayer on a metal surface. By chance, Anderson's experimental article was published simultaneously

[†] None of the major institutions in the U.S. are providing basic information about protection from Fukushima's radioactive fallout. Eating foods produced before the arrival of the radioactive rain, feeding old foods to chickens and milk animals, and keeping your metabolic rate high, are the main defenses. Eventually, fertilizing crops with mined minerals, and enriching the atmosphere with carbon from coal will dilute the radioactive isotopes from the nuclear accidents.

with Dudley's theoretical article, though neither one knew of the other's work.

Nearly all physicists said his results weren't possible, because the small forces involved in adsorbing an oil to a metal surface were infinitesimal compared to the force needed to cause nuclear reactions. Over the next few years, Dudley and others did some experiments that appeared to confirm Anderson's results, showing that the rate of nuclear reactions can be modified by mild changes in the physical state of the unstable elements.

Anderson's and Dudley's work didn't get much attention from the public, so there was no need for the defenders of the dominant paradigm to attack it. There was no financial support for continuing their research.

Behind the industries' assurances that "low level" radiation is safe, whether it's ionizing radiation, microwave or broadcast frequency electromagnetic radiation, is their reductionist approach to physics, chemistry, and biology. Those doctrines no longer have the prestige that they once did, but their pathological, authoritarian "science" culture is being sustained by the influence of corporations on mass culture.

With the institutions of research and education controlled by pharmaceutical, military and industrial interests for their own benefit, fundamental progress in knowledge is a threat to the system.

Phosphate, Activation, and Aging

Ray Peat's Newsletter, 2013

RECENT publications are showing that excess phosphate can increase inflammation, tissue atrophy, calcification of blood vessels, cancer, dementia, and, in general, the processes of aging. This is especially important, because of the increasing use of phosphates as food additives.

Previously, the complications of chronic kidney disease, with increased serum phosphate, were considered to be specific for that condition, but the discovery of a phosphate-regulating gene named klotho (after one of the Fates in Greek mythology) has caused a lot of rethinking of the biological role of phosphate. In the 19th century, phosphorus was commonly called brain food, and since about 1970, its involvement in cell regulation has become a focus of reductionist thinking. ATP, adenosine triphosphate, is seen as the energy source that drives cell movement as well as the "pumps" that maintain the living state, and as the source of the cyclic AMP that is a general activator of cells, and as the donor of the phosphate group that activates a great number of proteins in the "phosphorylation cascade." When tissues calcified in the process of aging, calcium was blamed (ignoring the existence of calcium phosphate crystals in the tissues), and low calcium diets were recommended. Recently, when calcium supplements haven't produced the intended effects, calcium was blamed, disregarding the other materials present in the supplements, such as citrate, phosphate, orotate, aspartate, and lactate.

I have a different perspective on the "phosphorylation cascade," and on the other functions of phosphate in cells, based largely on my view of the role of water in cell physiology. In the popular view, a stimulus causes a change of shape in a receptor protein, causing it to become an active enzyme, catalyzing the transfer of a phosphate group from ATP to another protein, causing it to change shape and become activated, and to transfer phosphate groups to other molecules, or to remove phosphates from active enzymes, in chain reactions. This is standard biochemistry, that can be done in a test tube.

Starting around 1970, when the involvement of phosphorylation in the activation of enzymes in glycogen breakdown was already well known, people began noticing that the glycogen phosphorylase enzyme

became active immediately when the muscle cell contracted, and that phosphorylation followed the activation. Phosphorylation was involved in activation of the enzyme, but if something else first activated the enzyme (by changing its shape), the addition of the phosphate group couldn't be considered as causal, in the usual reductionist sense. It was one participant in a complex causal process. I saw this as a possible example of the effect of changing water structure on protein structure and function. This view of water questions the relevance of test tube biochemistry.

Enzymes are known which suddenly become inactive when the temperature is lowered beyond a certain point. This is because soluble proteins arrange their shape so that their hydrophobic regions, the parts with fat-like side-chains on the amino acids, are inside, with the parts of the chain with water-soluble amino acids arranged to be on the outside, in contact with the water. The "wetness" of water, its activity that tends to exclude the oily parts of the protein molecule, decreases as the temperature decreases, and some proteins are destabilized when the relatively hydrophobic group is no longer repelled by the surrounding cooler water.

In the living cell, the water is all within a very short distance of a surface of fats or fat-like proteins. In a series of experiments, starting in the 1960s, Walter Drost-Hansen showed that, regardless of the nature of the material, the water near a surface is structurally modified, becoming less dense, more voluminous. This water is more "lipophilic," adapting itself to the presence of fatty material, as if it were colder. This change in the water's properties also affects the solubility of ions, increasing the solubility of potassium, decreasing that of sodium, magnesium, and calcium.[1]

When a muscle contracts, its volume momentarily decreases.[2] Under extremely high pressure, muscles contract. In both situations, the work-producing process of contraction is associated with a slight reduction in volume. During contraction of a muscle or nerve, heat is given off, causing the temperature to rise. During relaxation, recovering from excitation, heat is absorbed.[3–5] In the case of a nerve, following the heating produced by excitation, the temperature of the nerve decreases below the starting temperature.[6] Stretching a muscle causes energy to be absorbed.[5] Energy changes such as these, without associated chemical

changes, have led some investigators to conclude that muscle tension generation is "entropy driven."[7]

Kelvin's description (1858) of the physics of water in a soap bubble, "…if a film such as a soap-bubble be enlarged…it experiences a cooling effect…," describes the behavior of nerves and muscles, absorbing energy or heat when they are relaxing (or elongating), releasing it when they are excited/contracting.

Several groups of experimenters over the last 60 years have tried to discover what happens to the missing heat; some have suggested electrical or osmotic storage, and some have demonstrated that stretching generates ATP, arguing for chemical storage. Physical storage in the form of structural changes in the water-protein-lipid system, interacting with chemical changes such as ATP synthesis, have hardly been investigated.

Early studies of muscle chemistry and contraction found that adding ATP to a viscous solution of proteins extracted from muscle reduced its viscosity, and also that the loss of ATP from muscle caused its hardening, as in rigor mortis; if the pH wasn't too acidic, the dead muscle would contract as the ATP content decreased. Szent-Györgyi found that a muscle hardened by rigor mortis became soft again when ATP was added.

Rigor mortis is an extreme state of fatigue, or energy depletion. Early muscle studies described the phenomenon of "fatigue contracture," in which the muscle, when it reaches the point at which it stops responding to stimulation, is maximally contracted (this has also been called delayed relaxation). Ischemic contracture, in the absence of blood circulation, occurs when the muscle's glycogen is depleted, so that ATP can no longer be produced anaerobically.[8] The delayed relaxation of hypothyroid muscle is another situation in which it is clear that ATP is required for relaxation. (In the Achilles tendon reflex test, the relaxation rate is visibly slowed in hypothyroidism.) A delayed T wave in the electrocardiogram, and the diastolic contracture of the failing heart show the same process of delayed relaxation. Supplementing the active thyroid hormone, T_3, can quickly restore the normal rate of relaxation, and its beneficial effects have been demonstrated in heart failure.[9–12]

A large part of the magnesium in cells is bound to ATP, and the magnesium-ATP complex is a factor in muscle relaxation. A deficiency of either ATP or magnesium contributes to muscle cramping. When a cell is stimulated, causing ATP to release inorganic phosphate, it also

releases magnesium. Above the pH of 6.7, phosphate is doubly ionized, in which state it has the same kind of structural effect on water that magnesium, calcium, and sodium have, causing water molecules to be powerfully attracted to the concentrated electrical charge of the ion. Increasing the free phosphate and magnesium opposes the effect of the surfaces of fats and proteins on the water structure, and tends to decrease the solubility of potassium in the water, and to increase the water's "lipophobic" tendency to minimize its contacts with fats and the fat-like surface of proteins, causing the proteins to rearrange themselves.

These observations relating to the interactions of water, solutes and proteins in muscles and nerves provide a coherent context for understanding contraction and conduction, which is lacking in the familiar descriptions based on membranes, pumps, and cross-bridges, but I think they also provide a uniquely useful context for understanding the possible dangers of an excess of free phosphate in the body.

A few people (M. Thomson, J. Gunawardena, A.K. Manrai) are showing that principles of mass-action help to simplify understanding the networks of phosphorylation and dephosphorylation that are involved in cell control. But independently from the phosphorylation of proteins, the presence of phosphate ion in cell water modifies the cell's ion selectivity, shifting the balance toward increased uptake of sodium and calcium, decreasing potassium, tending to depolarize and "activate" the cell.

About 99 % of the publications discussing the mechanism of muscle contraction fail to mention the presence of water, and there's a similar neglect of water in discussions of the energy producing processes in the mitochondrion. The failure of mitochondrial energy production leads to lipid peroxidation, activation of inflammatory processes, and can cause disintegration of the energy producing structure. Increased phosphate decreases mitochondrial energy production,[13] causes lipid peroxidation,[14] and activates inflammation, increasing the processes of tissue atrophy, fibrosis, and cancer.

For about twenty years it has been clear that the metabolic problems that cause calcium to be lost from bones cause calcium to increase in the soft tissues, such as blood vessels. The role of phosphate in forming calcium phosphate crystals had until recently been assumed to be passive, but some specific "mechanistic" effects have been identified. For example, increased phosphate increases the inflammatory cytokine, osteopontin,[15] which in bone is known to activate the process of de-

calcification, and in arteries is involved in calcification processes.[16] In the kidneys, phosphate promotes calcification,[17] and osteopontin, by its activation of inflammatory T-cells, is involved in the development of glomerulonephritis, as well as in inflammatory skin reactions.[18] High dietary phosphate increases serum osteopontin, as well as serum phosphate and parathyroid hormone, and increases the formation of tumors in skin.[19]

Besides the activation of cells and cell systems, phosphate (like other ions with a high ratio of charge to size, including citrate) can activate viruses.[20,21] Aromatase, the enzyme that synthesizes estrogen, is an enzyme that's sensitive to the concentration of phosphate.[22]

More generally, increased dietary phosphate increases the activity of an important regulatory enzyme, protein kinase B, which promotes organ growth. A high phosphate diet increases the growth of liver[23] and lung,[24] and promotes the growth of lung cancer.[25] An extreme reduction of phosphate in the diet wouldn't be appropriate, however, because a phosphate deficiency stimulates cells to increase the phosphate transporter, increasing the cellular uptake of phosphate, with an effect similar to the dietary excess of phosphate, i.e., promotion of lung cancer.[26] The optimum dietary amount of phosphate, and its balance with other minerals, hasn't been determined.

While increased phosphate slows mitochondrial energy production, decreasing its intracellular concentration increases the respiratory rate and the efficiency of ATP formation. A "deficiency" of polyunsaturated fatty acids has this effect,[27] but so does the consumption of fructose.[28,29]

In a 1938 experiment[30] that intended to show the essentiality of unsaturated fats, a man, William Brown, lived for six months on a 2500 calorie diet consisting of sucrose syrup, a gallon of milk (some of it in the form of cottage cheese), and the juice of half an orange, besides some vitamins and minerals. The experimenters remarked about the surprising disappearance of the normal fatigue after a day's work, as well as the normalization of his high blood pressure and high cholesterol, and the permanent disappearance of his frequent life-long migraine headaches. His respiratory quotient increased (producing more carbon dioxide), as well as his rate of resting metabolism. I think the most interesting part of the experiment was that his blood phosphate decreased. In two measurements during the experimental diet, his fasting plasma inorganic phosphorus was 3.43 and 2.64 mg/dL of plasma, and six month

after he had returned to a normal diet the number was 4.2 mg/dL. Both the deficiency of the "essential" unsaturated fatty acids, and the high sucrose intake probably contributed to lowering the phosphate.

In 2000, researchers who were convinced that fructose is harmful to the health, reasoned that its harmful effects would be exacerbated by consuming it in combination with a diet deficient in magnesium. Eleven men consumed, for six months, test diets with high fructose corn syrup or starch, along with some fairly normal U.S. foods, and with either extremely low magnesium content, or with slightly deficient magnesium content. The authors' conclusion was clearly stated in the title of their article, that the combination adversely affects the mineral balance of the body.

However, looking at their results in the context of these other studies of the effects of fructose on phosphate, I don't think their conclusion is correct. Even on the extremely low magnesium intake, both their magnesium and calcium balances were positive, meaning that on average their bodies accumulated a little magnesium and calcium, even though men aged 22 to 40 presumably weren't growing very much. To steadily accumulate both calcium and magnesium, with the calcium retention much larger than the magnesium, the minerals were probably mostly being incorporated into their bones. Their phosphate balance, however, was slightly negative on the "high fructose" diet. If the sugar was having the same effect that it had on William Brown in 1938 (and in animal experiments), some of the phosphate loss was accounted for by the reduced amount in blood and other body fluids, but to continue through the months of the experiment, some of it must have represented a change in the composition of the bones. When there is more carbon dioxide in the body fluids, calcium carbonate can be deposited in the bones.[31] Increased carbon dioxide could account for a prolonged negative phosphate balance, by taking its place in the bones in combination with calcium and magnesium.

Another important effect of carbon dioxide is in the regulation of both calcium and phosphate, by increasing the absorption and retention of calcium,[32] and by increasing the excretion of phosphate. Increased carbon dioxide (as dissolved gas) and bicarbonate (as sodium bicarbonate) both increase the excretion of phosphate in the urine, even in the absence of the parathyroid hormone. Below the normal level of serum bicarbonate, reabsorption of phosphate by the kidneys is greatly

increased.[33] Acetazolamide increases the body's retention of carbon dioxide, and increases the amount of phosphate excreted in the urine.

Much of the calcium dissolved in the blood is in the form of a complex of calcium and bicarbonate, with a single positive charge.[34] Failure to consider this complexed form of calcium leads to errors in measuring the amount of calcium in the blood, and in interpreting its physiological effects, including its intracellular behavior. Hyperventilation can cause cramping of skeletal muscles, constriction of blood vessels, and excitation of platelets and other cells; the removal of carbon dioxide from the blood lowers the carbonic acid, changing the state and function of calcium. Hyperventilation increases phosphate and parathyroid hormone, and decreases calcium.[35]

Since estrogen tends to cause hyperventilation, lowering carbon dioxide, its role in phosphate metabolism should be investigated more thoroughly. Work by Han, et al.[36] and Xu, et al.[37] showed that estrogen increases phosphate reabsorption by the kidney, but estrogen also increases cortisol, which decreases reabsorption, so the role of estrogen in the whole system has to be be considered.

This calcium solubilizing effect of bicarbonate, combined with its phosphaturic effect, probably accounts for the relaxing effect of carbon dioxide on the blood vessels and bronchial smooth muscles, and for the prevention of vascular calcification by the thyroid hormones.[38–40] Distensibility of the blood vessels and heart, increased by carbon dioxide, is decreased in hypothyroidism, heart failure, and by phosphate.

While fructose lowers intracellular phosphate, it also lowers the amount that the intestine absorbs from food,[41] and the Milne-Nielsen study suggests that it increases phosphate loss through the kidneys. The "anti-aging" protein, klotho, increases the ability of the kidneys to excrete phosphate,[42] and like fructose, it supports energy production and maintains thermogenesis.[43]

Lowering the amount of phosphate in the blood allows the parathyroid hormone to decrease. While the parathyroid hormone also prevents phosphate reabsorption by the kidneys, it causes mast cells to release serotonin (and serotonin increases the kidneys' reabsorption of phosphate), and possibly has other pro-inflammatory effects. For example, deleting the PTH gene compensates for the harmful (accelerated calcification and osteoporosis) effects of deleting the klotho gene, apparently by preventing the increase of osteopontin.[44]

Niacinamide is another nutrient that lowers serum phosphate,[45] by inhibiting intestinal absorption,[46] and also by reducing its reabsorption by the kidneys.[47] Niacinamide's reduction of free fatty acids by inhibiting lipolysis, protecting the use of glucose for energy, might be involved in its effect on phosphate (by analogy with the phosphate lowering action of a deficiency of polyunsaturated fatty acids). Aspirin is another antilipolytic substance[48] which stimulates energy production from sugar and lowers phosphate, possibly combined with improved magnesium retention.[49]

A diet that provides enough calcium to limit activity of the parathyroid glands, and that is low in phosphate and polyunsaturated fats, with sugar rather than starch as the main carbohydrate, possibly supplemented by niacinamide and aspirin, should help to avoid some of the degenerative processes associated with high phosphate: fatigue, heart failure, movement discoordination, hypogonadism, infertility, vascular calcification, emphysema, cancer, osteoporosis, and atrophy of skin, skeletal muscle, intestine, thymus, and spleen.[50–52] The foods naturally highest in phosphate, relative to calcium, are cereals, legumes, meats, and fish. Many prepared foods contain added phosphate. Foods with a higher, safer ratio of calcium to phosphate are leaves, such as kale, turnip greens, and beet greens, and many fruits, milk, and cheese. Coffee, besides being a good source of magnesium, is probably helpful for lowering phosphate, by its antagonism to adenosine.[53]

Although increased phosphate generally causes vascular calcification (increasing rigidity, with increased systolic blood pressure), when a high level of dietary phosphate comes from milk and cheese, it is epidemiologically associated with reduced blood pressure.[54]

Phosphate toxicity offers some interesting insights into stress and aging, helping to explain the protective effects of carbon dioxide, thyroid hormone, sugar, niacinamide, and calcium. It also suggests that other natural substances used as food additives should be investigated more thoroughly. Excessive citric acid, for example, might activate dormant cancer cells,[55] and has been associated with malignancy.[56] Nutritional research has hardly begun to investigate the optimal ratios of minerals, fats, amino acids, and other things in foods, and how they interact with the natural toxicants, antinutrients, and hormone disrupters in many organisms used for food.

Physiology Texts and the Real World

Ray Peat's Newsletter, 2014

A sentence taken out of context is likely to be misleading. A chemical equation that is concerned only with the reactants, catalyst, and product, can be misleading, and its industrial application is likely to produce devastation and pollution along with the intended product. In nature and industry, the reactants, products, and energy changes are linked to the ecology and to the economy. In physiological chemistry, events in the organism are linked to the environment so closely that food, water, air, soil, and pollution form a firmly linked functional system.

But "medical physiology" has evolved as a separate thing, in which formulas that describe specific situations are linked to each other by fragmentary schemes, terminology, and computer models. This jerry-built scheme is even more roughly set into a hypothetical environment of "the origin of life," "evolution," "inheritance," "society," and a few other perfunctory contextualizations that have no more relevance to the subject than do the literary epigraphs that are often used at the beginning of chapters in medical books, to signify that the author isn't just a technical hack.

This physiological mythology has made possible a practice of medicine in which "genes" and "a virus" are regularly invoked to explain things that can't be remedied, and in which any fleshy body is described as "well nourished," and in which malnutrition and poisoning by pollutants are systematically dismissed as explanations for sicknesses, while thousands of different drugs are administered according to instructions given by their salesmen. It is also deeply linked to attitudes that have turned the practice of medicine into the surest way for an individual to get rich and retire early. It creates a sense of confidence that the

Hospital accidents kill more people than highway accidents. But when people die while they are receiving standard, but irrational and antiscientific treatments and "support," the deaths aren't counted as accidents. The numbers are large.

Medical training and medical textbooks bear great responsibility for those unnecessary deaths. Most medical research is done under the influence of mistaken assumptions, and so fails to correct the myths of medical training. If the "consumers" or victims of medicine are willing to demand concrete justifications before accepting "standard procedures," they will create an atmosphere in which medical mythology will be a little harder to sustain.

physician is doing the right thing, because there is a little physiological rationale for everything. When a practice is replaced by its opposite, there is also a rationale for that. In fact, medical textbooks are written to rationalize the highly arbitrary practices of the industry. If, for some reason, perpetual motion machines had been as successful economically as steam engines were, laws of thermodynamics would have been written to describe them, just as thermodynamic laws were invented to describe the theory of steam engines.

It was odd and interesting when a vice presidential candidate stepped to the podium several years ago and asked "who am I? What am I doing here?" But those questions are really of the greatest importance and interest, and physiology should be an attempt to understand more fully what we are, what we are doing, and how we are doing it. When we have comprehensive answers to those questions, then we will be in a position to create systematically valid solutions for our problems.

For physiology, the equivalent of medicine's "first do no harm" would be "first, don't believe unfounded doctrines." Accepting that principle puts a person into a critical attitude, and experiments can become actually "empirical," an extension of experience that allows you to perceive new things, rather than "testing hypotheses." Unless a hypothesis is a generalization from real experience, rather than a deduction from a doctrine, progress is likely to be very slow. A first step in developing a critical attitude is to identify the idols that stand in the way of real understanding.

Immunity, intelligence, appetites, tumor growth, aging, the proper development of organs—everything that we think of as the biological foundations of health and sickness—will be misinterpreted if there are fundamental misconceptions about physiology.

Physiology is the study of the vital functions of organisms, but especially when talking about "pathologic physiology," great emphasis in physiology textbooks is given to the processes that maintain homeostasis of the milieu interieur, or the constancy of composition of the "fluid in which tissue cells are bathed." Since cells are embedded in a gel-like matrix, "connective tissue," the connective tissue should have some serious attention in physiology courses, but in practice its composition is described, and then the rest of physiology treats it as the "extracellular space." Only specialists in the extracellular matrix are likely to take it seriously as a factor in physiology.

If medical physiologists are likely to think of cells as being "bathed in fluid" which fills the empty spaces around the cells, they are also likely to think of the cell's interior as a watery solution which "fills the space enclosed by the cell membrane." It is this image of the organism that has made traditional biochemistry possible, since enzymes extracted from cells and dissolved in water had been thought to function the way they function in the living state. But the living cell isn't like a tiny water-filled test-tube.

Some of the points that should be considered in a realistic (and therefore coherent) physiology text:

- Connective tissues, ground substance—making a multicell organism—secreting the right amount, modifying/maintaining it, responding to the scaffolding—where the crucial milieu interieur is.
- Cellular energy, a structural idea—a finely organized catalyst, a readiness for work, and conditions that determine the equilibrium of reactions.
- The dimensions of the organism range from cellular fields to organismic intentions, via functional systems.

Physiology should be understood in terms of its geochemical setting, because otherwise basic definitions will be built up in the belief that life is discontinuous from its physical environment, separated by membranes, and maintained by the expense of energy mainly to preserve gradients across those membranes; while in actuality the chemical energy released by living substance is spent in renewing structures, and the gradients are mainly passive physical-chemical consequences of structure. The spontaneous polymerization that occurs under volcanic conditions creates substances with intrinsic functions. The living state is a substance that is always being renewed as it interacts with its environment, and from the larger perspective, it is an evolving catalyst that modifies the environment so that the whole system approaches equilibrium with the energy that flows through it. Since the evolving system stores energy in its structure, the cosmic energy sources and sinks are at the boundaries of the system, and are the only questions that (so far) transcend the issue of life in its environment. The chemistry of the planet is tied up with cosmic energy, but the nature of the system as a whole is still relatively

unexplored. If plants are bracketed by the sun, carbon dioxide and water, animals are bracketed by sugar and oxygen.

- Acid-base regulation—selectivity; physical chemistry of coral, bone; kidney, lung; roles of oxygen, carbon dioxide and protein.
- An Arrhenius base is something which produces hydroxide ions when it's dissolved in water.
- Metal, an element that forms a base by combining with a hydroxyl group (or groups).
- Base, an electropositive element (cation) that combines with an anion to form a salt; a compound ionizing to yield hydroxyl ion.
- Electropositive atoms tend to lose electrons.
- Electronegative atoms, such as oxygen, chlorine, and fluorine, tend to take up an electron and to become negatively ionized.
- Definitions of Arrhenius and Lewis for acids and bases. It's important to keep both sides of an ionizable compound in mind, and to pay more attention to electrons than to protons.
- A Lewis acid is an electron acceptor.
- Alkali reserve, (Stedman's phrase:) "the basic ions, mainly the bicarbonates" (bicarbonates of this or that; there is no abstract "bicarbonate.")
- Carbon dioxide is a neutral Lewis acid, that associates with the hydroxide ion. (This observation may be shocking to people who have thought too long in terms of abstract "bicarbonate.")
- Carbon dioxide regulates water, minerals, energy and cellular stability, excitation, and efficiency.
- Cellular respiration regulates both energy and substance disposition.
- Respiration regulates osmotic/oncotic pressure, including the hydration (and dehydration) of the extracellular matrix.
- Electrons, positive charges, electronegativity, and induction: The unity of metabolism and signalling interactions; hormones are physical-chemical agents, not information carriers. Electrets, piezoelectricity, and crystal/bond stresses are relevant to physiology; the behavior of ionic materials in bulk water provides misleading images for physiology. Space charges are more relevant to physiology than fluxes in ion channels.

- Inductive effect: an electronic effect transmitted through bonds in an organic compound due to the electronegativity of substituents.
- Cooperative adsorption interacts with inductive effects producing coherent, systemic changes and stabilities.
- Steroids, peptides, biogenic amines, and other things considered as hormones and transmitters, are active as modifiers of adsorption, induction, and metabolic pathways. Their structural effects create, or inhibit, phase transitions in cells. Synergies of radiation, estrogen, and hypoxia are intelligible in terms of phase instability.
- Alkaloids: organic substances occurring naturally, which are basic, forming salts with acids. The basic group is usually an amino function.
- The disposition of electrons in cells and tissues is a global phenomenon, integrating metabolism, pH, osmolarity, and sensitivity. Excitation creates a field of alkalinity.
- Cellular differentiation; developmental fields, polarities.
- Regulation of water; electroosmosis; edema in relation to cellular energy.
- Vicinal water, all water near surfaces, most of the water in cells, has special properties.
- Needs on the cellular level guide the organism's adaptations.
- Functional systems, multilevel adaptive integrations, in which many "systems" and cell types are organized according to activity and needs, leading to anatomical and functional changes.
- Energy and relaxation, cellular inhibition, a structural state involving the entire cell substance. High energy phosphate bonds explain nothing about the cell's energy.
- Multilevel self-regulation; cell intelligence, organic compensations (function producing structure, organ regeneration, vascular neogenesis, stem cell functions, immunity/morphogenesis, tubercles/tumors, fat/fiber/muscle/phagocytosis) permits highly organized and novel adaptive responses, which are goal-directed rather than mechanistically "programmed" from the genes.
- Sensitivity and motility—plants and animals, subtle cues, rhythms, motivations.
- Adaptation—learning, intention, and stress.
- Light, energy, motion; pigments and electron donor-acceptor bonds.

- Acceptor of action, innate and learned models of reality. Intentionality is involved in "reflexes."
- Digestion—bowel and liver; immune system and nervous system; need and intepretation, analysis; approximation and assimilation. Intestinal flora and detoxifying. Detoxifying fatty acids, estrogen, insulin, nerve chemicals, etc.
- Nutrition—appetite and satisfaction.
- Reproduction, puberty, menopause; how they are affected by the environment.
- Humor, curiosity, exploratory and inventive potentials and need.
- Growth and aging; energy, individualization and generalization; mitosis and meiosis, germ cells.
- Nurse cells, their interactions in various organs.
- Chalones, wound hormones, phagocytes, regeneration, nerve products; inhibition of growth by nerves. Frog extracts in development. Anatomy is a dynamic system, whose integration is part of physiology.
- Inflammations and tumors are systemic events, in causes and effects.
- Inflammation, edema, fibrosis, calcification, and atrophy—the basic pathology.
- Organisms relate to the biosphere as factors in the creation of new equilibria.

Between 1947 and 1956, Arthur C. Guyton, of Ole Miss, wrote a textbook of medical physiology, and one of his students, J. E. Hall, has added chapters to it. It is the most widely used physiology textbook in the world. It may be more influential than the bible, since it has shaped the behavior of millions of doctors, affecting billions of people. Its success probably has something to do with Guyton's unusual personal experience. After graduating from Harvard Medical School and, along with others from Harvard, working in germ warfare,[†] he contracted polio, and returned to Mississippi. As someone moving from the centers of excellence and power to the most backward state in the nation, instead of using textbooks he wrote handouts for the classes he taught there, devising what he thought were plausible explanations for everything in physiology. A personalized perspective and desire to keep things simple made the book, based on those handouts, readable and popular.

The circulatory system, and the movement of fluids in the body, are at the center of physiology, so it is of interest that Guyton believed that, in the "spaces around cells," there is a negative pressure, a partial vacuum, that sucks fluid out of the capillaries. He believed that this suction would balance a column of 5 or 10 mm of mercury. The rib cage, and the force of the diaphragm muscle, can maintain a negative pressure around the lungs, preventing their elastic collapse, but there is no such shell around the rest of the body; if elastic fibers of connective tissue could be anchored to such a shell, then such a suction/vacuum would be conceivable.

Hydrostatic and osmotic pressures interact in tissues, but even the hydrostatic forces produced by the heartbeat are known only approximately, as estimates, on the microscopic level. The belief in subatmospheric interstitial pressure is unreasonable on its face, and measurements are so inaccurate in the microcirculation that its disproof would be somewhat like proving that fairies aren't responsible for the Brownian motions seen under a microscope.

The oncotic/osmotic behavior of proteins in the blood and extracellular (the term interstitial implies the presence of empty spaces which aren't really there) fluid is usually, in medical physiology, assumed to be a fixed quantity determined by the nature of the polymer. Swelling and syneresis (contraction) of gels, with the absorption or release of water, are strongly influenced by the electrical properties of the system, which includes solvent water, bound water, and small solutes and ions as well as the polymers. Changes in pH and ionic strength and temperature, and the presence of solutes modifying the polymer's affinity for water, affect the osmotic behavior of the polymer, and of gels formed by such polymers. Since the extracellular spaces are mainly filled with solid gels, Guyton's image of simple fluids entering and leaving these "spaces" reveals a major conceptual error, and that error has been widely propagated by medical professors. If a person imagines open spaces, interstices, between cells, then the question of the fluid pressure in these chambers seems reasonable, and the factors that produce edema will be thought of mechanically. But if we call the material between cells the "extracellular matrix," and recognize its relatively solid gel nature, we

will see the problem of edema in physical-chemical terms, rather than as a problem of simple hydraulics.

Idols of medical physiology, foundations and cornerstones for the landfill, some things you shouldn't know about physiology:

- Genes control the cell, the organism is its genome, the nucleus regulates the cytoplasm. Information flowing from the genes produces and maintains the organism.
- Acquired traits aren't passed on; mutations are random, the genome doesn't acquire information from the organism or environment, the germ-line is isolated.
- Physiology is bounded by the informational function of genes.
- The cell is a drop of water containing dissolved chemicals enclosed in a membrane.
- Random diffusion governs energy metabolism, gene induction, and other intracellular events.
- Enzyme reactions occur when dissolved molecules randomly diffusing come into contact with a suitable enzyme, as described by the Michaelis-Menton equation.
- The Donnan equilibrium explains cellular electrical behavior, and since ions are distributed across the membrane by active transport, the membrane potential is maintained by the expense of metabolic energy.
- Water is just a peculiar solvent.
- Water structure changes only at extremes of temperature.
- Cells are perfect osmometers.
- There are empty spaces between cells.

† Biographical side-lights: Guyton graduated from Ole Miss in 1939, got his medical degree from Harvard in 1943, where the department of bacteriology had a grant to study the polio virus, and where he worked with people "involved in the war effort," and then from 1944 to 1946 was involved in germ warfare research, mainly at Camp Detrick. Camp Detrick had been established as the center for chemical and biological warfare research, and a test site was established in Mississippi in 1943. Guyton's first paper was on aerosol research (published in 1946), and studies at that time were being done to improve the spreading of germs in aerosols. Bacterial aerosols were tested on the public in San Francisco, in 1950. Guyton's Harvard colleagues established a polio research lab at Children's Hospital Medical Center. When he left the navy, after working at Camp Detrick, Guyton resumed work at Mass General, and contracted polio before he finished his residency.

- The membrane regulates the composition of the cytoplasm, with pumps and pores and channels. Cells must produce enough energy to keep the pumps running.
- Membrane receptors regulate cell responses.
- Cells are activated by receptors, and physical forces for which there are no receptors have no effect on cells except when they are above a threshold at which they cause discrete chemical changes.
- The nervous system is hard-wired.
- Brain and heart cells don't regenerate.
- There is an immune system, whose function is to destroy pathogens, with inflammation as one of its functions, and its specific reactions are determined by the selection of clones which were generated by random mutations; an autonomic nervous system, which regulates visceral reflexes by innervating, via receptors, smooth muscle, heart muscle, and glands; an endocrine system, regulated mainly by negative feedback, that produces hormone molecules that carry messages to the receptors in certain target tissues.
- Inflammation is produced by germs, and is a defensive reaction of the immune system, and so is good. (Sterile inflammation is too confusing to include within the ambit of medical physiology, since it is associated with serious harm to the organism. The roles in inflammation of the nervous and endocrine systems and kidneys and membrane pumps and osmoregulation aren't discussed in polite books.)
- During development, cells are organized into systems, and they don't change their type. In the case of germ cells, their type is determined before they exist. Cells are able to undergo only about 50 divisions, and most of those divisions are used up in producing an adult organism.
- The committed nature of the organism's cells and anatomy make radical functional adaptation impossible.
- Hormones and transmitter substances act only through specific receptor molecules.
- High energy phosphate bonds in compounds such as ATP provide energy to molecular pumps and motors.
- Molecular forces act only locally.

- Pathologies are primarily local: Inflammations and tumors have local causes, and their effects are local. Specific and local treatments are ideal. Circulation is treated as a plumbing problem, tumors as clones of defective cells.
- Consciousness is produced by nervous signals that transmit information, and can be compared with the handling of information by computers.
- Excitation and inhibition are functions of cell membranes.
- Artificial intelligence research into computational and nerve net systems is as much a part of research into the physiology of consciousness as computer modeling of feedback systems is a form of research into endocrine physiology and immunology.
- Estrogen, testosterone, thyroid, prolactin, serotonin, adrenalin, prostaglandins, etc., are carriers of information in an informational system.
- Cyclic functions and behaviors are governed by genes.
- The existence of hard-wired informational receptor systems and gene-induction systems is necessary because of the random diffusional nature of the other cellular processes and materials.
- Essentially, an organism consists of random inert matter given form and activity by the imposition of genetic information accumulated through random mutations.

(There are really people who still believe those things.)

A Note on Scientific Revolutions

If scientific revolutions depended on "the authorities," then the Copernican revolution would be dated from the Pope's apology. The fact that the major journals are controlled by antiscientific dimwits helps to define where science exists. Gilbert Ling's revolution in cell physiology has been moved along by the existence of the journal, Physiological Chemistry and Physics (and medical NMR).

Michael Polanyi, in *Personal Knowledge*, maybe even more than Thomas Kuhn did in his famous book (*Structure of Scientific Revolutions*), helped to solidify the belief that there is a real international monolithic "community of science." Even though Polanyi, working "in isolation" in Hungary created his general and elegant adsorption isotherm, he didn't

teach it to his own students, because of his belief in that community of science, which ridiculed his work because it wasn't based on their (false) assumptions about the electrical nature of matter.

The linguistic and cultural isolation of Hungary and Russia from Europe has permitted them to evolve distinctive scientific cultures. C.C. Lindegren, in Cold War in Biology, showed that political forces in the U.S. and England suppressed anti-Mendelian ideas by identifying them as subversive, imposing the Central Dogma of genetics. But even within an authoritarian national tradition, there are little communities of science, where the real development of thought can take place.

Perceptions that are clear and useful are the real revolutions in science, and the rest of it has to do with social and financial commitments.

Even in the short time since Kuhn wrote his book, the status of medicine has changed significantly, putting it right up with militarism and the energy industry as a source of political and economic power. The authoritarian monolith that has been known as the community of science has become increasingly (even in areas such as astronomy, where commercial interests aren't so crudely involved) a structure of cultural propaganda maintained by bullying and fraud. Since the "normal science" in these authoritarian settings is dedicated to evading the truth, it becomes almost a guide to where to look for the truth. It's sort of analogous to the "mystery" of why breast cancer mortality is lowest in the poorest part of the U.S., Appalachia, and highest in the richest regions: the medical industry goes where the money is, taking death with it. Science, like health, thrives on the neglect of the corrupt industry.

I have always felt that the cybernetic definition of communication as the transfer of something that makes a difference should be applied to speech and writing. As a student and teacher, I saw that information which made a difference was the essence of intellectual excitement and growth. But making a difference is exactly what university administrators and journal editors don't want.

Preventing and Treating Cancer with Progesterone

Ray Peat's Newsletter, 2007

> "The energy of the mind is the essence of life."
>
> — Aristotle

All through the last century, as more and more resources were devoted to solving "the cancer problem," the death rate from cancer increased every year. Something was clearly wrong with the way the problem was being approached.

If you grind up a computer and dissolve it in acid, you can find out exactly what substances it was made of, but you won't learn from that information how the computer worked. Twentieth century biologists became fond of emulsifying cells and studying the soluble parts. By the end of the century, they had identified so many parts that the government was financing projects to use supercomputers to try to understand how the parts interacted.

If some essential information was lost in studying the parts, supercomputation isn't the way to find it. Even with infinite computing capacity, a description of the electrons on carbon and hydrogen atoms on amino acids in protein molecules won't lead to the reality of how those atoms would have functioned in the living state.

The image of a cell as a watery solution contained in an elastic membrane bag is still having a radically stupefying effect on biology and medicine. The idea that a cell can be understood by using a computer to model a network of interactions between genes and gene products is nothing more than a technologizing of the primitive understanding of life that was promulgated by the Weismann-Mendel-Morganist school. It was the dogmatic insistence of that genetic determinist school that cancer originated with a genetic mutation.

By the middle of the 20th century, that dogma had excluded the most important parts of biology from the schools and the journals. Ideas of a developmental field, cellular coherence, and holistic cooperativity were denounced as unscientific vitalism. Returning to the idea of a "cancer

field" is an essential first step in thinking realistically about preventing and treating cancer, but that idea has hardly progressed since the 1930s.

In the last few years, interest in cloning and stem cells and tissue regeneration has revived interest in studying the factors that contribute to the spatial and temporal ordering of cell growth.

The idea of a developmental field was a fundamental part of embryology in the first half of the 20th century. It was an empirical idea, supported most commonly by evidence that diffusing substances and secreted materials governed the differentiation of cells and tissues, but the form-generating effects of bioelectric fields were also often demonstrated, and there was some evidence that tissue radiations played a role. The extracellular matrix secreted by cells served to transmit information between cells, but its form was regulated by cells, and its structure was a factor governing the cells' differentiation.

Experiments in amphibians showed that regeneration of organs had a reciprocal relationship with the development of cancer—a tumor could be turned into a tail, for example, if it was grafted onto the stump following amputation of the tail, but factors that weakened regeneration could cause a tumor to develop. In these experiments, the normal organism's morphogenetic or epimorphic field overrode the disordered developmental field of the tumor.

In the absence of overriding external influences, the disordered system of the tumor, in which cells emitted many products of their disordered metabolism, could interfere with the normal functions of the organism. All of the products of the injured cells, including their altered extracellular matrix, constituted the cancer field.

The recent recognition of the "bystander effect" of radiation exposure, in which cells that haven't been irradiated undergo genetic changes or death when they are exposed to irradiated cells, has provided an opportunity to return to the "field" idea in cancer, because the stress-induced factors emitted by irradiated cells are the same toxic factors emitted by cells undergoing carcinogenesis from other causes, such as over-exposure to estrogen.

H. J. Muller, one of T. H. Morgan's students and colleagues, studied the mutagenic effects of x-rays, and the genetic determinists argued that the random changes produced in the genetic material by ionizing radiation provided a model of the evolutionary process. Randomly altered genes and natural selection would explain everything, including cancer.

Every time cells divide, their genes supposedly become more susceptible to random changes, so increased replication of cells would increase the risk of producing genetic changes leading to cancer. This idea is so simple and so widely believed that many people focus only on the rate of proliferation, and the random mutations that supposedly occur during proliferation, when they try to explain carcinogenesis. They feel that it's reasonable to discuss cancer without bothering to understand the physiology of the cell or the organism.

The organism can only be understood in its environments, and a cell can't be understood without reference to the tissue and organism in which it lives. Although the geneticists were at first hostile to the idea that nutrition and geography could have anything to do with cancer, they soon tried to dominate those fields, insisting that mutagens and ethnicity would explain everything. But the evidence now makes it very clear that environment and nutrition affect the risk of cancer in ways that are not primarily genetic.

Every tumor, like every person, has a uniqueness, but valid and practical empirical generalizations can be made, if we understand some of their properties and the conditions that govern their development and survival.

Percival Potts' observation of scrotal cancer in chimney sweeps eventually led to the study of soot carcinogenesis, and then to the study of the properties of the polycyclic aromatic hydrocarbons in soot. The similarities of those properties to estrogen's soon became apparent.

Over the decades, many studies have confirmed that prolonged, continuous exposure to estrogen is carcinogenic, and that progesterone offsets those effects.

Following the animal studies that showed that carcinogenesis by estrogen could be prevented or reversed by progesterone, studies of the endogenous hormones in women showed that those with a natural excess of estrogen, and/or deficiency of progesterone, were the most likely to develop uterine or breast cancers.

The Morganist school of genetic determinism moved into endocrinology with a doctrine that hormones act only through hormone receptors, proteins which activate certain genes.

Many researchers—physical chemists, biochemists, cytologists, embryologists, reproductive and developmental biologists, gerontologists, physiologists, neurologists, endocrinologists—were investigating estro-

gen's properties and actions, and had made great progress by the 1950s, despite the medical frauds being perpetrated by the estrogen industry.[1]

All of this complex and subtle work was of no interest to a small group of people who wanted to impose their genetic views onto biology.

The inventor of the estrogen receptor, Elwood Jensen, has written that the results of certain of his experiments "caused the demise of the transhydrogenation hypothesis and convinced all but the most diehard enzymologists that estradiol binds to a characteristic component of target cells to exert its physiological effect without itself being chemically altered." The hypothesis he referred to was just part of a large fairly systematic international effort.

How he did away with the opposition, who were studying the complex metabolic actions of estrogen, was by synthesizing isotope-labeled estradiol and estrone, and claiming to observe that they weren't metabolically altered, as they produced their hormonal effect. Since the experiment was extremely expensive, and required the cooperation of the Atomic Energy Commission, it wasn't easily repeated. However, many experiments have subsequently demonstrated that practically every tissue in the body (and plants and bacteria) metabolize the estrogens, causing estradiol to change into estrone, and estrone, into estradiol. Jensen's decisive and historically crucial experiment was false.

But it served its purpose, and (with help from the pharmaceutical industry and government granting agencies) marginalized the work of those "enzymologists" and everyone else who persisted in studying the complex actions of estrogen.

The enzyme that converts the weaker estrone into the stronger estradiol is an important factor in determining estrogen's effects on a particular tissue. Progesterone is able to regulate the cell's metabolism, so that the oxidative pathway, forming estrone from estradiol, predominates. Estrogen-dominated tissues are likely to have a balance in the direction of reduction rather than oxidation, increasing the amount of the active estradiol.

The immediate effects of estrogen and progesterone on cells, that occur long before genes can be activated, were simply ignored or denied by the promoters of the estrogen receptor doctrine. Some of these excitatory or antiexcitatory effects are probably structural changes, that involve the mobilization of calcium inside cells, and the activation or inhibition of reactions involving phosphoric acid. Although they have

been known for many years, they are always referred to as "novel" or "non-classical" effects, and are called "membrane effects," because that's the only way the reductionists are able to identify changes that happen immediately throughout the cell.

Cellular excitation involves an increase of intracellular calcium and the activation of phosphorylating enzymes in cells. Some experiments suggest[2] that the estrogen receptor mediates estrogen's ability to mobilize calcium (leading to the activation of cell division, mitosis). Whether or not it does, the recognition that estrogen activates calcium, leading to activation of the phosphorylation system, should "cause the demise of" the "classical estrogen receptor" doctrine, because the phosphorylation system alters the expression of genes, much as the estrogen receptor was supposed to do by its direct actions. But before it alters the expression of genes, it alters the activities of enzymes. When estrogen activates calcium and phosphorylation independently of the estrogen receptor, the situation is even worse for the Jensen dogma.

Progesterone's opposition to those early excitatory effects of estrogen are so basic, that there shouldn't be any difficulty in thinking of it as an antiestrogen, that stops cell division primarily by opposing the excitatory effects of estrogen and other mitogens. Progesterone's opposition to the calcium-activating and phosphorylating effects of estrogen affects everything in the cell, according to the cell's specific nature.

But the reductionists don't like "nongenomic" explanations of anything, even when they are triggered by the estrogen receptor rather than by a membrane-event. So, to argue that progesterone's opposition to estrogen is general, it's necessary to examine each of estrogen's actions, where those actions are clearly known, and to evaluate progesterone's effects on the same events.

When a cell is stimulated or slightly stressed, homeostatic mechanisms are activated that help it to return to its normal resting state. The mobilization of calcium and the phosphorylation system is followed by increased synthesis of cholesterol and the formation of glucose from glycogen. Cholesterol itself is protective, and in some cells it is massively converted into progesterone, which is even more effective in restoring homeostasis.

In the ovary, the enzymes that synthesize cholesterol, along with the production of progesterone, are activated by the pituitary hormone, FSH, but also by estrogen. In the liver and uterus and vascular endothelium,

which aren't specialized for the production of progesterone, stimulation by estrogen activates the enzymes to increase the formation of cholesterol.

When cells are injured or seriously stressed, instead of being able to directly recover their normal quiescence, they may instead mobilize their systems for growing and replicating, to replace damaged or destroyed cells.

Prolonged exposure to estrogen, that can't be offset by the homeostatic factors, such as progesterone, typically causes cells to enter a growth phase. (But so do other excitatory processes, such as ionizing radiation.)

One of the basic reactions to injury is to shift the cell away from oxidative metabolism to glycolytic metabolism, which is inefficient, but can support cell division. Chemical stains show that during cell division cells are in a reduced state, with abundant sulfhydryl groups including reduced glutathione and protein sulfhydryls. This shift in itself increases the formation of active estradiol from estrone.

In the inflamed or estrogen dominated cell, enzymes such as the cyclooxidases (COX), that convert arachidonic acid into prostaglandins, are activated. Beta-glucuronidase and sulfatases are activated, and these cause intracellular estrogen to increase, by removing the water soluble sulfate and glucuronate portions from estrogens that had been inactivated. The detoxifying enzymes that attach those molecules to estrogen are inactivated in the estrogen dominated cell. The prostaglandin formed from arachidonic acid stimulates the formation of the enzyme aromatase or estrogen synthetase, that converts androgens into estrogen.

Those processes, initiated by excitation or injury, increase the amount of estrogen in the cell, which intensifies the excitation.

Progesterone opposes all of those processes, decreasing the amount of estrogen in the cell by modifying the activities of those five types of enzyme.

Although many kinds of protein (including enzymes) bind estrogen, the protein that Jensen called "the estrogen receptor" is largely responsible for the ability of the uterus and breasts to retain high concentrations of estrogen. Various kinds of stimulation or stress (including heat and oxygen deprivation) cause its appearance, and estrogen itself increases the amount of the estrogen receptor in a cell. The estrogen receptor doesn't just "activate genes," as the Jensen dogma claimed. For

example, the estrogen receptor directly binds and inactivates the "tumor suppressor" p53 protein, which otherwise would restrain the replication of damaged cells.

Progesterone causes the estrogen receptor to be eliminated. (Batra; Boling and Blandau; Resko, et al.)

Among the cell activating factors, other than estrogen, are proteins that are considered to be "oncogenes," because of their involvement in cancer. Several of these proteins are activated by estrogen, inhibited by progesterone. The term "oncogene" refers to any gene that contributes to the development of cancer, but it is so burdened by ideology that it shouldn't be used as if it had a simple clear meaning.

A variety of proteins promote cell activity and replication, under the influence of estrogen. The "composite transcription factor activating protein 1," AP-1 which integrates the effects of other transcription factors, is important in a variety of cell types, and its activity is increased by estrogen and decreased by progesterone.

When the "progesterone receptor" lacks progesterone, it has the opposite effect of progesterone, and this feature has been used propagandistically, by infecting cells with a virus carrying the progesterone receptor protein, and then suggesting that the disturbed functions of the cell reflect a potential effect of progesterone. The receptor, lacking progesterone, tells the cell that it has a progesterone deficiency, but too many molecular endocrinologists are trying to say that the receptor protein is the same as the progesterone.

The generality of the process of excitation/activation can be clearly seen in the effects of the nerve-inhibiting GABA and the nerve-exciting glutamate or NMDA. In cultured breast cancer cells, GABA inhibits growth, NMDA increases growth. As in the brain, progesterone supports the actions of GABA, and opposes those of NMDA or the excitatory amino acids, while estrogen in general promotes the effects of the excitatory amino acids, and opposes those of GABA.

Both the excitatory amino acids and a peptide that promotes inflammation, tumor necrosis factor (TNF), activate the enzyme which makes estrogen, aromatase. Estrogen, by activating NF kappaB, increases the formation of TNF, which in itself can promote the growth and metastasis of cancer. Various antiinflammatory agents, including aspirin, progesterone, testosterone, saturated fats, and glycine, can inhibit the production of NF kappaB.

An enzyme that has been thought of mainly in relation to the brain is catechol-O-methyl transferase, which is inhibited by estrogen (producing effects similar to cocaine), leading to brain excitation.The enzyme detoxifies catecholestrogen,[3] protecting cells from DNA damage.[4] When the activity of this enzyme is low, there is increased risk of breast cancer.[5] Progesterone increases its activity ([6,7]).

Another enzyme system that affects the body's reactions to stress and modifies processes of inflammation and growth, the monoamine-oxidases, is affected oppositely by estrogen and progesterone. Estrogen's effects are partly mediated by increased formation of serotonin, progesterone's, by decreasing it. Histamine is another promoter of inflammation that is increased by estrogen, decreased by progesterone.

Estrogen's effects in the nervous system go beyond the production of cocaine-like hypomania, or chorea, or epilepsy, and include the activation of the basic stress hormones, increasing the formation in the hypothalamus of pro-opiomelanocortin (POMC), which is a precursor of ACTH to activate the adrenals, and endorphins ("endogenous opiates"), which stimulate growth processes. Both endorphins and ACTH can be found in tumors such as breast cancer. The ACTH stimulates the production of cortisol, that protects against some of the immediate causes of inflammation and growth, but that contributes to the loss of resistance, and increases estrogen synthesis.

A protein called the sigma receptor, known for its role in cocaine's action, binds progesterone, and can inhibit the growth of cancer. Some anesthetics have similar effects on tumors, acting through this protein. The sigma receptor, in association with progesterone or pregnenolone, is protective against the excitatory amino acids.

The extracellular medium changes during the development of a tumor. Irritated hypoxic cells, and estrogen-stimulated cells, increase their production of collagen, and the increase of collagen interferes with normal cell functions. Progesterone reduces the formation of collagen, and probably contributes to its removal.

Naloxone or naltrexone, which blocks the actions of the endorphins and morphine, is being used to inhibit the growth of various kinds of cancer, including breast cancer and prostate cancer. Leptin (which is promoted by estrogen) is a hormone produced by fat cells, and it, like estrogen, activates the POMC-related endorphin stress system. The

endorphins activate histamine, another promoter of inflammation and cell division.

Progesterone opposes those various biochemical effects of estrogen in multiple ways, for example by inhibiting the ACTH stress response, by restraining cortisol's harmful actions, and by inhibiting leptin.

Mediators of the radiation bystander effect include NO, TNF, COX, and prostaglandins. These are produced by other things that cause inflammation and injury, including estrogen.

Cell division, when it is part of the body's continuous renewal and adaptation, isn't a source of mutations or degeneration, but when it is induced by the mediators of inflammation produced in response to injury, it leads to inherited changes, loss of differentiated function, and eventually to genetic instability.

When cell division is so disturbed that the number of chromosomes becomes abnormal, the instability of these cells decreases their ability to survive, but when the causes of the inflammation persist, they will continue to be replaced by other abnormal cells. The toxic products of dying cells can reach a point at which the debris can't be removed, adding to the injury and inflammation. The damaged bystander cells spread their influence through a cancer field, injuring more cells.

One of the "field" effects of cancer is the stimulation of new blood vessel development, angiogenesis. Lactic acid stimulates the formation of new blood vessels, the secretion of collagen, and tumor growth. Low oxygen, nitric oxide, carbon monoxide, prostaglandins and other products of tissue stress can stimulate the growth of new blood vessels, at the same time that they stimulate tumor growth and impair oxidative metabolism. Several of these agents promote each other's activity.

Therapeutic thinking has been influenced by the doctrine of the mutant cell as the initiator of cancer, leading to the idea that only things which kill the cancer cells can cure cancer. But when the body stops activating the processes of inflammation and growth, normal processes of tissue repair have an opportunity to eliminate the tumor. Even the fibroblasts which normally secrete collagen can participate in its removal.[8] Something as simple as eliminating lactate can change their functions.

Although the angiogenic action of lactate has been known for several decades, some researchers believed that a specific anti-angiogenic peptide could be found which would stop the growth of cancer cells. The interest in angiogenesis tacitly acknowledges that there is a cancer field,

but the faith that cancer could be cured only by killing the mutant cells seems to have guided the search for a single antiangiogenic substance. Such a substance would be toxic to normal tissues, since blood vessels are constantly being renewed.

The more advanced a tumor is, the more numerous the growth-promoting factors are likely to be, and the weaker the body's ability becomes to control them.

The search for toxic factors to kill the cancer cells is unlikely to lead to a generally effective treatment. Even immunological approaches that think in terms of destroying a tumor might be misconceiving the nature of the problem. For example, the protein called "tumor necrosis factor" (TNF) or cachectin was discovered as a result of Lawrence Burton's work in the 1960s. He extracted proteins from the blood that could shrink some tumors in mice with amazing speed. In the right setting, TNF is involved in the destruction of tumors, but when other factors are missing, it can make them worse. Burton was focussing on factors in the immune system that could destroy cancer, but he ignored the basic problem of tissue degeneration that produces tumors which are complex and changing.

If the cancer-productive field is taken into account, all of the factors that promote and sustain that field should be considered during therapy.

Two ubiquitous carcinogenic factors that can be manipulated without toxins are the polyunsaturated fatty acids (PUFA) and estrogen. These closely interact with each other, and there are many ways in which they can be modulated.

For example, keeping cells in a well oxygenated state with thyroid hormone and carbon dioxide will shift the balance from estradiol toward the weaker estrone. The thyroid stimulation will cause the liver to excrete estrogen more quickly, and will help to prevent the formation of aromatase in the tissues. Low temperature is one of the factors that increases the formation of estrogen. Lactic acid, serotonin, nitric oxide, prostaglandins, and the endorphins will be decreased by the shift toward efficient oxidative metabolism.

Progesterone synthesis will be increased by the higher metabolic rate, and will tend to keep the temperature higher.

Thyroid hormone, by causing a shift away from estrogen and serotonin, lowers prolactin, which is involved in the promotion of several kinds of cancer.

Vitamin D and vitamin K have some antiestrogenic effects. Vitamin D and calcium lower the inflammation-promoting parathyroid hormone (PTH).

Eliminating polyunsaturated fats from the diet is essential if the bystander effect is eventually to be restrained. Aspirin and salicylic acid can block many of the carcinogenic effects of the PUFA. Saturated fats have a variety of antiinflammatory and anticancer actions. Some of those effects are direct, others are the result of blocking the toxic effects of the PUFA. Keeping the stored unsaturated fats from circulating in the blood is helpful, since it takes years to eliminate them from the tissues after the diet has changed. Niacinamide inhibits lipolysis. Avoiding over-production of lipolytic adrenaline requires adequate thyroid hormone, and the adjustment of the diet to minimize fluctuations of blood sugar.

The endorphins are antagonistic to progesterone, and when they are minimized, progesterone tends to increase, and to be more effective. The drugs naloxone and naltrexone, which block the effects of the endorphins, have several remarkable effects that resemble progesterone's. Naltrexone has been successfully used to treat prostate and breast cancer.

Opiates are still commonly used for pain relief in cancer patients, despite the evidence that has accumulated for several decades indicating that they promote inflammation and cancer growth, while suppressing immunity and causing tissue catabolism, exacerbating the wasting that commonly occurs with cancer. Their use, rather than alternatives such as procaine, aspirin, and progesterone, is nothing but a medical fetish.

Stress and estrogen tend to produce alkalosis, while thyroid, carbon dioxide, and adequate protein in the diet help to prevent alkalosis.

Antihistamines and some of the antiserotonin drugs (including "dopaminergic" lisuride and bromocriptine) are sometimes useful in cancer treatment, but the safe way to lower serotonin is to reduce the consumption of tryptophan, and to avoid excessive cortisol production (which mobilizes tryptophan from the muscles). Pregnenolone and sucrose tend to prevent over-production of cortisol.

In the breast, COX-2 converts arachidonic acid into prostaglandins, which activate the enzyme aromatase, that forms estrogen from androgens. Until the tissues are free of PUFA, aspirin and salicylic acid can be used to stop prostaglandin synthesis.

Thyroid is needed to keep the cell in an oxidative, rather than reductive state, and progesterone (which is produced elsewhere only when

cells are in a rapidly oxidizing state) activates the processes that remove estrogen from the cell, and inactivates the processes that would form new estrogen in the cell.

Thyroid, and the carbon dioxide it produces, prevent the formation of the toxic lactic acid. When there is enough carbon dioxide in the tissues, the cell is kept in an oxidative state, and the formation of toxic free radicals is suppressed. Carbon dioxide therapy is extremely safe.

In the 1930s, primates as well as rodents had been used in experiments to show the carcinogenic effects of estrogen, and the protective effects of progesterone.

By 1950, the results of animal studies of progesterone's anticancer effects were so clear that the National Cancer Institute got involved. But the estrogen industry had already been conducting its campaign against progesterone, and had convinced most doctors that it was inactive when taken orally, and so was inferior to their proprietary drugs that they called "progestins." The result was that it was usually given by injection, dissolved in vegetable oil or synthetic solvents such as benzyl benzoate or benzyl alcohol, which are very toxic and inflammation-producing.

The NCI researchers[9] treated 17 women with visible cancers of the uterine cervix that had been confirmed by biopsies. They were given daily intramuscular injections of 250 mg of progesterone in vegetable oil. Although they described the treatment as "massive dosage with progesterone," it didn't prevent menstruation in any of the women who had been menstruating before the treatment began. During a healthy pregnancy, a woman produces more progesterone than that.

Their article includes some photographs of cervical tumors before treatment, and after 31 days, 50 days, and 65 days of progesterone treatment. The improvement is clear. The examining physicians described softening of the tumor, and stopping of bleeding and pain.

"In eleven of the 17 treated patients visible and palpable evidence of regressive alteration of the tumor mass could be demonstrated. This consisted of (a) distinct reduction in size of the visible portion of the cancer as well as reduction of the palpable extent of the mass, (b) reduction in vascularity and friability of the visible lesion with a clearly demonstrable epithelization of previously raw surfaces and (c) markedly increased pliability of the previously rigid and infiltrated parametria."

"In 10 cases there was associated with this type of gross change a reduction in, or complete cessation of vaginal bleeding and discharge."

"Only one of the 17 patients showed active progression of the carcinomatous process while under the progesterone administration. The six patients whose lesions failed to show clearly demonstrable regressive changes showed minor alterations in size and vascularity of insufficient degree to be convincing to all clinical observers concerned. Nevertheless, none of the lesions under study appeared to be accelerated by progesterone."

Observing very similar patients under similar conditions while they were waiting for surgery, but were not receiving progesterone, they saw no such regressions of tumors.

The photographs and descriptions of the changes in the tumors were remarkable for any cancer study, but to have been produced by a treatment that didn't even alter the patients' menstrual cycle, the reader might expect the authors to discuss their plans for further studies of such a successful method.

But instead, they concluded "We do not consider the regressive changes observed to be sufficient to indicate the use of progesterone as a therapeutic agent in carcinoma of the cervix."

(Their research was supported by a grant from the American Cancer Society.)

If the researchers had bothered to test progesterone on themselves or on animals, they would have discovered that it is fully active when taken orally, dissolved in oil, and that nontoxic saturated fats could have been used. Progesterone anesthesia was very well known at that time, so it would have been reasonable to use doses that were at least equivalent to the concentrations present during pregnancy, even if they didn't want to use doses that would approach the anesthetic level. The total daily doses could have been about ten times higher, if they had been given orally as divided doses.

The solvent issue continues to impede research in the use of progesterone for treating cancer, but the main problem is the continuing belief that "the cancer cell" is the problem, rather than the cancer field. Substances are tested for their ability to kill cancer cells in vitro, because of the basic belief that mutated genes are the cause of the disease. When progesterone is tested on cancer cells *in vitro*, the experimenter often sees nothing but the effects of the solvent, and doesn't realize that nearly all of the progesterone has precipitated in the medium, before reaching the cancer cells.

The cancer industry began a few years ago to combine chemicals for chemotherapy, for example adding caffeine to paclitaxel or platinum (cisplatin), or histamine to doxorubicin, but they do it simply to increase the toxicity of the chemical to the tumor, or to decrease its toxicity to the patient. Doctors sometimes refer to combined chemotherapy as a "shotgun approach," meaning that it lacks the acumen of their ideal silver bullet approach. If cancers were werewolves, the cancer industry's search for more refined killing technologies might be going in the right direction. But the genetic doctrine of cancer's origin is just as mythical as werewolves and vampires.

A safe physiological approach to cancer, based on the opposition of progesterone to estrogen, would be applicable to every type of cancer promoted by estrogen, or by factors which produce the same effects as estrogen, and that would include all of the known types of cancer. Estrogen acts even on cells that have no "estrogen receptors," but estrogen receptors can be found in every organ.

As estrogen's non-feminizing actions are increasingly being recognized to include contributions to other kinds of disease, including Alzheimer's disease, heart disease, and rheumatoid arthritis, the idea of the bystander effect, and the field of cellular degeneration, will eventually clear the way for a rational use of the therapeutic tools that already exist.

There are several types of drug—carbonic anhydrase inhibitors, to increase carbon dioxide in the tissues, lysergic acid derivatives, to block serotonin and suppress prolactin, anti-opiates, antiexcitotoxic and GABAergic agents, anesthetics, antihistamines, anticholinergics, salicylic acid derivatives—that could probably be useful in a comprehensive therapy for cancer, but their combinations won't be explored as long as treatments are designed only to kill.

Preventing or correcting disturbances in the morphogenetic field should be the focus of attention.

Progesterone, Not Estrogen, is the Coronary Protection Factor of Women

Ray Peat's Newsletter, 2006

In the 1940s, around the time that Hans Selye was reporting that estrogen causes shock, and that progesterone protects against many stress-related problems, the anthropologist Ashley Montague published The Natural Superiority of Women. Later, as I looked at the history of endocrine research, it seemed apparent that progesterone was responsible for many of the biological advantages of females, such as a longer average life-span, while testosterone was responsible for men's advantage in muscular strength.

Although evidence of estrogen's toxicity had been accumulating for decades, pharmaceutical promotion was finding hundreds of things to treat with estrogen, which they called "the female hormone." By the 1940s, it was known to produce excessive blood clotting, miscarriage, cancer, age-like changes in connective tissue, premenstrual syndrome, varicose veins, orthostatic hypotension, etc., but, as Mark Twain said, a lie can run around the world before the truth gets its boots on.

After the DES fiasco, in which "the female hormone" which had been sold to prevent miscarriages was proven to cause them, the estrogen industry decided to offer men the protection against heart attacks that women supposedly got from their estrogen. The men who received estrogen in the study had an increased incidence of heart attacks, so that campaign was postponed for about 30 years.

The Shutes used vitamin E to treat the excessive blood clotting caused by estrogen, and vitamin E was considered to be an estrogen antagonist. Estrogen affected the liver's production of clot-regulating proteins, and it also relaxed large veins, allowing blood pooling that slowed the blood sufficiently to give it time to form clots before returning to the lungs. Early in the century, unsaturated fats were found to inactivate the proteolytic enzymes that dissolve clots, and vitamin E was known, by the 1940s, to provide protection against the toxicity of the unsaturated fats. The toxic synergy of estrogen and unsaturated fats had already been recognized.

But in the 1950s, the seed oil industry, ignoring the toxic, carcinogenic effects of the unsaturated oils, began intensified promotion of

their products as beneficial foods. (Decades earlier, Mark Twain had reported on the plans of the cottonseed industry to make people eat their by-product instead of butter.)

While estrogen was being offered as the hormone that protects against heart attacks, the liquid vegetable oils were being advertised as the food that would prevent heart attacks. Just a few years after the estrogen industry suffered the setbacks of the DES and heart attack publicity, the oil industry cancelled some tests of the "heart protective diet," because it was causing both more heart attacks and more cancer deaths.

Somehow, these two fetid streams converged: Estrogen, like the unsaturated oils, lowered the amount of cholesterol in the blood, and an excess of blood cholesterol was said to cause heart attacks. (And, more recently, the estrogenic effects of the seed oils are claimed to offer protection against cancer.)

The ability to lower the cholesterol "risk factor" for heart attacks became a cultural icon, so that the contribution of estrogen and unsaturated oils to the pathologies of clotting could be ignored. Likewise, the contribution of unsaturated fats' lipid peroxidation to the development of atherosclerotic plaques was simply ignored. But one of estrogen's long established toxic effects, the reduction of tone in veins, was turned into something like a "negative risk factor": The relaxation of blood vessels would prevent high blood pressure and its consequences, in this new upside down paradigm. This vein-dilating effect of estrogen has been seen to play a role in the development of varicose veins, in orthostatic hypotension, and in the formation of blood clots in the slow-moving blood in the large leg veins.

When it was discovered that the endothelial relaxing factor was nitric oxide, a new drug business came into being. Nitroglycerine had been in use for decades to open blood vessels, and, ignoring the role of nitrite vasodilators in the acquired immunodeficiency syndrome, new drugs were developed to increase the production of nitric oxide. The estrogen industry began directing research toward the idea that estrogen works through nitric oxide to "improve" the function of blood vessels and the heart.

(Besides the argument based on "risk factors," many people cite the published observations that "women who take estrogen are healthier"

than women who don't use it. But studies show that their "control groups" consisted of women who weren't as healthy to begin with.)

In the 1970s, after reading Szent-Györgyi's description of the antagonistic effect of progesterone and estrogen on the heart, I reviewed the studies that showed that progesterone protects against estrogen's clotting effect. I experimented with progesterone, showing that it increases the muscle tone in the walls of veins, which is very closely related to the effects Szent-Györgyi described in the heart. And progesterone opposes estrogen's ability to increase the amount of free fatty acids circulating in the blood.

More recently, it has been discovered that progesterone inhibits the expression of the enzyme nitric oxide synthase, while estrogen stimulates its expression. At the time of ovulation, when estrogen is high, a woman breathes out 50 % more nitric oxide ("NO") than men do, but at other times, under the influence of increased progesterone and thyroid, and reduced estrogen, women exhale much less NO than men do. (Nitric oxide is a free radical, and it decomposes into other toxic compounds, including the free radical peroxynitrile, which damages cells, including the blood vessels. brain, and heart. Carbon dioxide tends to inhibit the production of peroxynitrile.)

If nitric oxide produced under the influence of estrogen were important in preventing cardiovascular disease, then men's larger production of nitric oxide would give them greater protection than women have.

From more realistic perspectives, nitric oxide is being considered as a cause of aging, especially brain aging. Nitric oxide interacts with unsaturated fats to reduce oxygen use, damage mitochondria, and cause edema.

I think we can begin to see that the various "heart protective" ideas that have been promoted to the public for fifty years are coming to a dead end, and that a new look at the fundamental problems involved in heart disease would be appropriate. Basic principles that make heart disease more understandable will also be useful for understanding shock, edema, panic attacks, high altitude sickness, high blood pressure, kidney disease, some lung diseases, MS, multiple organ failure, and excitotoxicity or "programmed" cell death of the sort that causes degenerative nerve diseases and deterioration of other tissues.

The research supporting this view is remarkably clear, but it isn't generally known because of the powerful propaganda coming from the drug and oil industries and their public servants.

Broda Barnes was right when he said that the "riddle of heart attacks" was solved when he demonstrated that hypothyroidism caused heart attacks, and that they were prevented by correcting hypothyroidism. He also observed that correcting hypothyroidism prevented the degenerative conditions (including heart disease) that so often occur in diabetics. Since hypothyroidism and diabetes are far more frequent in women, who have fewer heart attacks than men, it is appropriate to wonder why women tolerate hypothyroidism better than men.

In hypothyroidism and diabetes, respiration is impaired, and lactic acid is formed even at rest, and relatively little carbon dioxide is produced. To compensate for the metabolic inefficiency of hypothyroidism, adrenalin and noradrenalin are secreted in very large amounts. Adrenalin causes free fatty acids to circulate at much higher levels, and the lactic acid, adrenalin, and free fatty acids all stimulate hyperventilation. The already deficient carbon dioxide is reduced even more, producing respiratory alkalosis. Free fatty acids, especially unsaturated fats, increase permeability of blood vessels, allowing proteins and fats to enter the endothelium and smooth muscle cells of the blood vessels. Lactic acid itself promotes an inflammatory state, and in combination with reduced CO_2 and respiratory alkalosis, contributes to the hyponatremia (sodium deficiency) that is characteristic of hypothyroidism. This sodium deficiency and osmotic dilution causes cells to take up water, increasing their volume.

In hyperventilation, the heart's ability to work is decreased, and the work it has to do is increased, because peripheral resistance is increased, raising blood pressure. One component of peripheral resistance is the narrowing of the channels in blood vessels caused by endothelial swelling. In the heart, a similarly waterlogged state makes complete contraction and complete relaxation impossible.

Estrogen itself intensifies all of these changes of hypothyroidism, increasing permeability and edema, and decreasing the force of the heart-beat, impairing the diastolic relaxation. Besides its direct actions, and synergism with hypothyroidism, estrogen also chronically increases growth hormone, which causes chronic exposure of the blood vessels to higher levels of free fatty acids (with a bias toward unsaturated fatty

acids), and promotes edema and vascular leakage. Hyperestrogenism, like hypothyroidism, tends to produce dilution of the body fluids, and is associated with increased bowel permeability, leading to endotoxemia; both dilution of the plasma and endotoxemia impair heart function.

Progesterone's effects are antagonistic to estrogen's. Progesterone decreases the formation of nitric oxide, decreasing edema; it strengthens the heart beat, by improving venous return and increasing stroke volume, but at the same time it reduces peripheral resistance by relaxing arteries (by inhibiting calcium entry but also by other effects, and independently of the endothelium) and decreasing edematous swelling.

The effects of progesterone on the heart and blood vessels are paralleled by those of carbon dioxide: Increased carbon dioxide increases perfusion of the heart muscle, increases its stroke volume, and reduces peripheral resistance. The physical and chemical properties of carbon dioxide that I have written about previously include protective anti-excitatory and energy-sustaining functions that explain these effects. Since these effects have been known for many years, I think it is obvious that the obsessive interest in explaining these functions in terms of other molecules, such as nitric oxide, is motivated by the desire for new drugs, not by a desire to understand the physiology with which the researchers are pretending to deal.

Although women, because of estrogen's antithyroid actions, are much more likely to suffer from hypothyroidism than men are, until menopause they have much higher levels of progesterone than men do. The effects of hyperestrogenism and hypothyroidism, with lower carbon dioxide production, are offset by high levels of progesterone. After menopause, women begin to have heart attacks at a rapidly increasing rate.

During the years that men are beginning to have a considerable risk of heart attacks, with declining thyroid function indicated by lower T_3, their testosterone and progesterone are declining, while their estrogen is rising. Men who have heart attacks have much higher levels of estrogen than men at the same age who haven't had a heart attack.

Whether the issue is free radical damage, vascular permeability with fat deposition, vascular spasm, edema, decreased heart efficiency, or blood clotting, the effects of chronic estrogen exposure are counter-adaptive. Progesterone, by opposing estrogen, is universally protective against vascular and heart disease.

So far, the rule in most estrogen/progesterone research has been to devise experiments so that claims of benefit can be made for estrogen, with the expectation that they will meet an uncritical audience. In some studies, it's hard to tell whether idiocy or subterfuge is responsible for the way the experiment was designed and described, for example when synthetic chemicals with anti-progesterone activity are described as "progesterone." Since one estrogen-funded researcher who supposedly found progesterone to be ineffective as treatment for premenstrual syndrome practically admitted to me in conversation an intent to mislead, I think it is reasonable to discount idiocy as the explanation for the tremendous bias in published research. With the vastly increased resources in the estrogen industry, resulting from the product promotion "for the prevention of heart disease," I think we should expect the research fraud to become increasingly blatant.

Rather than being "heart protective," estrogen is highly heart-toxic, and it is this that makes its most important antagonist, progesterone, so important in protecting the heart and circulatory system.

Progesterone, Pregnenolone & DHEA

Three Youth-Associated Hormones

Ray Peat's Newsletter, 2006

Progesterone Information

SIXTY years ago, progesterone was found to be the main hormone produced by the ovaries. Since it was necessary for fertility and for maintaining a healthy pregnancy, it was called the "pro-gestational hormone," and its name sometimes leads people to think that it isn't needed when you don't want to get pregnant. In fact, it is the most protective hormone the body produces, and the large amounts that are produced during pregnancy result from the developing baby's need for protection from the stressful environment. Normally, the brain contains a very high concentration of progesterone, reflecting its protective function for that most important organ. The thymus gland, the key organ of our immune system, is also profoundly dependent on progesterone.

In experiments, progesterone was found to be the basic hormone of adaptation and of resistance to stress. The adrenal glands use it to produce their anti-stress hormones, and when there is enough progesterone, they don't have to produce the potentially harmful cortisone. In a progesterone deficiency, we produce too much cortisone, and excessive cortisone causes osteoporosis, aging of the skin, damage to brain cells, and the accumulation of fat, especially on the back and abdomen.

Experiments have shown that progesterone relieves anxiety, improves memory, protects brain cells, and even prevents epileptic seizures. It promotes respiration, and has been used to correct emphysema. In the circulatory system, it prevents bulging veins by increasing the tone of blood vessels, and improves the efficiency of the heart. It reverses many of the signs of aging in the skin, and promotes healthy bone growth. It can relieve many types of arthritis, and helps a variety of immunological problems.

If progesterone is taken dissolved in vitamin E, it is absorbed very efficiently, and distributed quickly to all of the tissues. If a woman has ovaries, progesterone helps them to produce both progesterone and estrogen as needed, and also helps to restore normal functioning of the

thyroid and other glands. If her ovaries have been removed, progesterone should be taken consistently to replace the lost supply. A progesterone deficiency has often been associated with increased susceptibility to cancer, and progesterone has been used to treat some types of cancer.

It is important to emphasize that progesterone is not just the hormone of pregnancy. To use it only "to protect the uterus" would be like telling a man he doesn't need testosterone if he doesn't plan to father children, except that progesterone is of far greater and more basic significance than testosterone. While men do naturally produce progesterone, and can sometimes benefit from using it, it is not a male hormone. Some people get that impression, because some physicians recommend combining estrogen with either testosterone or progesterone, to protect against some of estrogen's side effects, but progesterone is the body's natural complement to estrogen. Used alone, progesterone often makes it unnecessary to use estrogen for hot flashes or insomnia, or other symptoms of menopause.

When dissolved in vitamin E, progesterone begins entering the blood stream almost as soon as it contacts any membrane, such as the lips, tongue, gums, or palate, but when it is swallowed, it continues to be absorbed as part of the digestive process. When taken with food, its absorption occurs at the same rate as the digestion and absorption of the food.

Pregnenolone

Pregnenolone, which is the raw material for producing many of the hormones of stress and adaptation, was known as early as 1934, but for several years it was considered to be an "inert" substance. A reason for this belief is that it was first tested on healthy young animals. Since these animals were already producing large amounts of pregnenolone (in the brain, adrenal glands, and gonads), additional pregnenolone had no effect.

In the 1940s, pregnenolone was tested in people who were sick or under stress, and it was found to have a wide range of beneficial actions, but the drug industry never had much interest in it. Its very generality made it seem unlike a drug, and its natural occurrence made it impossible to patent. Thus, many synthetic variants, each with a more specialized action and some serious side effects, came to be patented and promoted

for use in treating specific conditions. The drug companies created an atmosphere in which many people felt that each disease should have a drug, and each drug, a disease. The side effects of some of those synthetic hormones were so awful that many people came to fear them. For example, synthetic varieties of "cortisone" can destroy immunity, and can cause osteoporosis, diabetes, and rapid aging, with loss of pigment in the skin and hair, and extreme thinning of the skin.

Natural pregnenolone is present in young people of both sexes at a very high concentration, and one reason for the large amount produced in youth is that it is one of our basic defenses against the harmful side effects that an imbalance of even our natural hormones can produce. In excess, natural cortisone or estrogen can be dangerous, but when there is an abundance of pregnenolone, their side effects are prevented or minimized.

In a healthy young person or animal, taking even a large dose of pregnenolone has no hormone-like or drug-like action at all. It is unique in this way. But if the animal or person is under stress, and producing more cortisone than usual, taking pregnenolone causes the cortisone to come down to the normal level. After the age of 40 or 45, it seems that everyone lives in a state of continuous "stress," just as a normal part of aging. This coincides with the body's decreased ability to produce an abundance of pregnenolone.

When aging rats are given a supplement of pregnenolone, it immediately improves their memory and general performance. Human studies, as early as the 1940s, have also demonstrated improved performance of ordinary tasks. It is now known that pregnenolone is one of the major hormones in the brain. It is produced by certain brain cells, as well as being absorbed into the brain from the blood. It protects brain cells from injury caused by fatigue, and an adequate amount has a calming effect on the emotions, which is part of the reason that it protects us from the stress response that leads to an excessive production of cortisone. People feel a mood of resilience and an ability to confront challenges.

Many people have noticed that pregnenolone has a "face-lifting" action. This effect seems to be produced by improved circulation to the skin, and by an actual contraction of some muscle-like cells in the skin. A similar effect can improve joint mobility in arthritis, tissue elasticity in the lungs, and even eyesight. Many studies have shown it to be protective

of "fibrous tissues" in general, and in this connection it was proven to prevent the tumors that can be caused by estrogen.

Pregnenolone is largely converted into two other "youth-associated" protective hormones, progesterone and DHEA. At the age of 30, both men and women produce roughly 30 mg to 50 mg. of pregnenolone daily. When taken orally, even in the powdered form, it is absorbed fairly well. One dose of approximately 300 mg (the size of an aspirin tablet) keeps acting for about a week, as absorption continues along the intestine, and as it is "recycled" in the body. Part of this long lasting effect is because it improves the body's ability to produce its own pregnenolone. It tends to improve function of the thyroid and other glands, and this "normalizing" effect on the other glands helps to account for its wide range of beneficial effects.

DHEA: Another Youth-Associated Hormone

DHEA (dehydroepiandrosterone) has a technical-sounding name because it has never been identified with a single dominant function, in spite of its abundance in the body. Many researchers still think of it as a substance produced by the adrenal glands, but experiments show that animals without adrenals are able to produce it in normal amounts. Much of it is formed in the brain (from pregnenolone), but it is probably produced in other organs, including the skin. The brain contains a much higher concentration of DHEA than the blood does.

In old age, we produce only about 5 % as much as we do in youth. This is about the same decrease that occurs with progesterone and pregnenolone. The other hormones (for example, cortisone) do not decrease so much; as a result, our balance shifts continually during aging toward dominance by hormones such as cortisone, which use up more and more body substance, without rebuilding it. Protection against the toxic actions of these specialized hormones is a major function of DHEA and the other youth-associated hormones.

For example, starvation, aging, and stress cause the skin to become thin and fragile. An excess of cortisone—whether it is from medical treatment, or from stress, aging, or malnutrition—does the same thing. Material from the skin is dissolved to provide nutrition for the more essential organs. Other organs, such as the muscles and bones, dissolve more slowly, but just as destructively, under the continued influence

of cortisone. DHEA blocks these destructive effects of cortisone, and actively restores the normal growth and repair processes to those organs, strengthening the skin and bones and other organs. Stimulation of bone-growth by DHEA has been demonstrated *in vitro* (in laboratory tests), and it has been used to relieve many symptoms caused by osteoporosis and arthritis, even when applied topically in an oily solution.

Estrogen is known to produce a great variety of immunological defects, and DHEA, apparently by its balancing and restorative actions, is able to correct some of those immunological defects, including some "autoimmune" diseases.

It is established that DHEA protects against cancer, but it isn't yet understood how it does this. It appears to protect against the toxic cancer-producing effects of excess estrogen, but its anti-cancer properties probably involve many other functions.

Diabetes can be produced experimentally by certain poisons which kill the insulin-producing cells in the pancreas. Rabbits were experimentally made diabetic, and when treated with DHEA their diabetes was cured. It was found that the insulin-producing cells had regenerated. Many people with diabetes have used brewer's yeast and DHEA to improve their sugar metabolism. In diabetes, very little sugar enters the cells, so fatigue is a problem. DHEA stimulates cells to absorb sugar and to burn it, so it increases our general energy level and helps to prevent obesity.

Young people produce about 12 mg to 15 mg of DHEA per day, and that amount decreases by about 2 mg per day for every decade after the age of 30. This is one of the reasons that young people eat more without getting fat, and tolerate cold weather better: DHEA, like the thyroid hormone, increases our heat production and ability to burn calories. At the age of 50, about 4 mg. of DHEA per day will usually restore the level of DHEA in the blood to a youthful level. It is important to avoid taking more than needed, since some people (especially if they are deficient in progesterone, pregnenolone, or thyroid) can turn the excess into estrogen or testosterone, and large amounts of those sex hormones can disturb the function of the thymus gland and the liver.

People who have taken an excess of DHEA have been found to have abnormally high estrogen levels, and this can cause the liver to enlarge, and the thymus to shrink.

One study has found that the only hormone abnormality in a group of Alzheimers patients' brains was an excess of DHEA. In cell culture, DHEA can cause changes in glial cells resembling those seen in the aging brain. These observations suggest that DHEA should be used with caution. Supplements of pregnenolone and thyroid seem to be the safest way to optimize DHEA production.

Progesterone Summaries

Progesterone Supplementation—Dosage of Progesterone

Ray Peat's Newsletter, 2007

Progesterone Information

SIXTY years ago, progesterone was found to be the main hormone produced by the ovaries. Since it was necessary for fertility and for maintaining a healthy pregnancy, it was called the "pro-gestational hormone," and its name sometimes leads people to think that it isn't needed when you don't want to get pregnant. In fact, it is the most protective hormone the body produces, and the large amounts that are produced during pregnancy result from the developing baby's need for protection from the stressful environment. Normally, the brain contains a very high concentration of progesterone, reflecting its protective function for that most important organ. The thymus gland, the key organ of our immune system, is also profoundly dependent on progesterone.

In experiments, progesterone was found to be the basic hormone of adaptation and of resistance to stress. The adrenal glands use it to produce their antistress hormones, and when there is enough progesterone, they don't have to produce the potentially harmful cortisol. In a progesterone deficiency, we produce too much cortisol, and excessive cortisol causes osteoporosis, aging of the skin, damage to brain cells, and the accumulation of fat, especially on the back and abdomen.

Experiments have shown that progesterone relieves anxiety, improves memory, protects brain cells, and even prevents epileptic seizures. It promotes respiration, and has been used to correct emphysema. In the circulatory system, it prevents bulging veins by increasing the tone of blood vessels, and improves the efficiency of the heart. It reverses many of the signs of aging in the skin, and promotes healthy bone growth. It can relieve many types of arthritis, and helps a variety of immunological problems.

If progesterone is taken dissolved in vitamin E, it is absorbed very efficiently, and distributed quickly to all of the tissues. If a woman has ovaries, progesterone helps them to regulate themselves and their hormone production. It helps to restore normal functioning of the

thyroid and other glands. If her ovaries have been removed, progesterone should be taken consistently to replace the lost supply. A progesterone deficiency has often been associated with increased susceptibility to cancer, and progesterone has been used to treat some types of cancer.

It is important to emphasize that progesterone is not just the hormone of pregnancy. To use it only "to protect the uterus" would be like telling a man he doesn't need testosterone if he doesn't plan to father children, except that progesterone is of far greafter and more basic physiological significance than testosterone. While men do naturally produce progesterone, and can sometimes benefit from using it, it is not a male hormone. Some people get that impression, because some physicians recommend combining estrogen with either testosterone or progesterone, to protect against some of estrogen's side effects, but progesterone is the body's natural complement to estrogen. Used alone, progesterone often makes it unnecessary to use estrogen for hot flashes or insomnia, or other symptoms of menopause.

When dissolved in vitamin E, progesterone begins entering the blood stream almost as soon as it contacts any membrane, such as the lips, tongue, gums, or palate, but when it is swallowed, it continues to be absorbed as part of the digestive process. When taken with food, its absorption occurs at the same rate as the digestion and absorption of the food.

Progesterone Supplementation

Symptomatic: For tendonitis, bursitis, arthritis, sunburn, etc., progesterone in vitamin E can be applied locally after a little olive oil has been put on the skin to make it easier to spread the progesterone solution. For migraines, it has been taken orally just as the symptoms begin.

For PMS: The normal pattern of progesterone secretion during the month is for the ovaries to produce a large amount in the 2nd two weeks of the menstrual cycle, (i.e., day 14 through day 28) beginning at ovulation and ending around the beginning of menstruation, and then to produce little for the following two weeks. An average person produces about 30 milligrams daily during the 2nd two weeks. The solution I have used contains approximately 3 or 4 mg of progesterone per small drop. Three to four drops, or about 10 mg to 15 mg of progesterone, is often enough to bring the progesterone level up to normal. That

amount can be taken days 14 through 28 of the menstrual cycle; this amount may be repeated once or twice during the day as needed to alleviate symptoms. Since an essential mechanism of progesterone's action involves its opposition to estrogen, smaller amounts are effective when estrogen production is low, and if estrogen is extremely high, even large supplements of progesterone will have no clear effect; in that case, it is essential to regulate estrogen metabolism, by improving the diet, correcting a thyroid deficiency, etc. (Unsaturated fat is antithyroid and synergizes with estrogen.)

Perimenopausal: The symptoms and body changes leading up to menopause are associated with decreasing production of progesterone, at a time when estrogen may be at a lifetime high. The cyclic use of progesterone, two weeks on, two weeks off, will often keep the normal menstrual cycle going. Three to four drops, providing ten or twelve milligrams of progesterone, is typical for a day, but some women prefer to repeat that amount. Progesterone is always more effective when the diet contains adequate protein, and when there isn't an excessive amount of unsaturated fat in the diet.

Postmenopausal: Some women continue the cyclic use of progesterone after menopause, because the pituitary gland and brain may continue to cycle long after menstruation has stopped, and progesterone is an important regulator of pituitary and brain function. The cycling pituitary affects the adrenal glands and other organs, and progesterone tends to protect against the unopposed actions of prolactin, cortisol, and adrenal androgenic hormones. Progesterone's effects on the pituitary apparently contribute to its protective effect against osteoporosis, hypertension, hirsutism, etc. But some women prefer to use progesterone without interruption after the menopause, for its protective antistress effects. Slender people usually find that two or three drops are enough, but this amount may be repeated once or twice as needed to relieve symptoms. Adequate protein in the diet and good thyroid function help the body to produce its own progesterone; even if the ovaries have been removed, the adrenal glands and brain continue to produce progesterone.

Dosage of Progesterone

Since progesterone has none of the harmful side effects of other hormones (except for alteration of the menstrual cycle if it is taken at the

wrong time of month), the basic procedure should be to use it in sufficient quantity to make the symptoms disappear, and to time its use so that menstrual cycles are not disrupted. This normally means using it only between ovulation and menstruation unless symptoms are sufficiently serious that a missed period is not important. The basic idea of giving enough to stop the symptoms can be refined by some information on a few of the factors that condition the need for progesterone.

If a person has an enlarged thyroid gland, progesterone promotes secretion and unloading of the stored "colloid," and can bring on a temporary hyperthyroid state. This is a corrective process, and in itself isn't harmful. A thyroid supplement should be used to shrink the goiter before progesterone is given. Normal amounts of progesterone facilitate thyroid secretion, while a deficiency, with unopposed estrogen, causes the thyroid to enlarge. The production of euphoria has been mentioned as a side effect, but I think euphoria is simply an indication of a good physiological state. (The history of official medical attitudes toward euphoria is a subject that deserves more attention.) Very large doses that are given in vitamin E solution, allowing complete absorption, can reach the level that is sometimes achieved late in pregnancy, producing both euphoria and a degree of anesthesia. To avoid unexpected anesthesia, the correct dose should be determined by taking about 10 mg. at a time allowing it to spread into the membranes of the mouth, and repeating the dose after 10 minutes until the symptoms are controlled.

An excessive estrogen/progesterone ratio is more generally involved in producing or aggravating symptoms than either a simple excess of estrogen or a deficiency of progesterone, but even this ratio is conditioned by other factors, including age, diet, other steroids, thyroid, and other hormones. The relative estrogen excess seems to act by producing tissue hypoxia (as reported in my dissertation, University of Oregon, 1972), and this is the result of changes induced by estrogen in alveolar diffusion, peripheral vascular changes, and intracellular oxygen wastage.

Hypoxia in turn produces edema (as can be observed in the cornea when it is deprived of oxygen, as by a contact lens) and hypoglycemia (e.g., diminished ATP acts like insulin), because glycolysis must increase greatly for even a small deficiency of oxygen. Elevated blood lactic acid is one sign of tissue hypoxia. Edema, hypoglycemia, and lactic academia can also be produced by other "respiratory" defects, including hypothyroidism, in which the tissue does not use enough oxygen. In

hypoxia, the skin will be bluer (in thin places, such as around the eyes), than when low oxygen consumption is the main problem. Low thyroid is one cause of excess estrogen, and when high estrogen is combined with low thyroid, the skin looks relatively bloodless.

Symptoms in cycling women are most common around ovulation and in the premenstrual week, when the estrogen/progesterone ratio is normally highest. At puberty, in the early twenties and in the late thirties and menopause are the ages when the ratio is most often disturbed—and these are also the ages when thyroid disorders are commonest in women.

The individual who suffers from one aspect of the progesterone (and/or thyroid) deficiency will tend to develop other problems at different times. With cyclic depressions or migraine headaches at age 22, there will possibly be breast disease lafter, and often there will be problems with pregnancy. These people with a history of sever symptoms are the ones most likely to have severe problems around menopause. Prenatal exposure to poorly balanced hormones seems to predispose the child to lafter hormone problems.

Excess stress (which can block progesterone synthesis and elevate estrogen) may bring on symptoms in someone who never had them. Spending a summer in Alaska, with an unusually long day, may relieve the symptoms of a chronic sufferer. Dark cloudy winters in England or the Pacific Northwest are powerful stressors, and cause lower production of progesterone in women, and testosterone in men. Toxins can produce similar symptoms, as can nutritional deficiencies. A very common cause of an estrogen excess is a dietary protein deficiency—the liver simply cannot detoxify estrogen when it is under-nourished.

With a diet high in protein (e.g., at least 70 g/day to 100 g/day, including eggs) and vitamin A (not carotene), I have found that the dose of progesterone can be reduced each month. Using thyroid will usually reduce the amount of progesterone needed. Occasionally, a woman won't feel any effect even from 100 mg. of progesterone; I think this indicates that they need to use thyroid and diet, to normalize their estrogen, prolactin, and cortisol.

Progesterone stimulates the ovaries and adrenals to produce progesterone, and it also activates the thyroid, so one dose can sometimes have prolonged effects. It shouldn't be necessary to keep using progesterone indefinitely, unless the ovaries have been removed. In slender post-

menopausal women, 10 mg/day is usually enough to prevent progesterone deficiency symptoms.

In a 10 % solution of progesterone in vitamin E, one drop contains about three milligrams of progesterone. Normally, the body produces 10 to 20 milligrams per day. A dose of 3 or 4 drops usually brings the blood levels up to the normal range, but this dose can be repeated several times during the day if it is needed to control symptoms.

For general purposes, it is most economical and effective to take progesterone dissolved in vitamin E orally, for example taking a few drops on the lips and tongue, or rubbing it into the gums. (It is good for the general health of the gums.) These membranes are very thin, and the progesterone quickly enters the blood. When it is swallowed, the vitamin E allows it to be absorbed through the walls of the stomach and intestine, and it can be assimilated along with food, in the chylomicrons, permitting it to circulate in the blood to all of the organs before being processed by the liver. These droplets are smaller than red blood cells, and some physicians seem to forget that red blood cells pass freely through the liver.

For the topical treatment of sun damaged skin, or acne, wrinkles, etc. the oil can be applied directly to the affected area.

Prostate Cancer

Ray Peat's Newsletter, 2013

It was noticed several decades ago that estrogen causes the prostate gland to enlarge in experimental animals, but by then an oversimplified view of the sex hormones was already well established, that led people to say that "estrogen causes the female organs to grow, and testosterone causes the male organs to grow." Logically extending this mistaken idea led many of the same people to suppose that the "hormones of one sex would inhibit the growth of the reproductive organs of the other sex."

When a friend of mine was told he had prostate cancer, though he had had no symptoms, and should receive large doses of estrogen, I reviewed the literature, to see whether his doctor might have seen something I had neglected. Since that time, I have found it necessary to use quotation marks around the phrases "medical research" and "medical science," because there is a certain kind of "research" performed within the medical profession which is peculiar to that profession.

When I read through the studies cited by the current articles as the basis for using estrogen to treat prostate cancer, I saw that the decisive "research" had consisted of mailing a questionnaire to physicians asking them if they thought it was reasonable to administer estrogen to these patients on the basis of its opposition to testosterone, which was considered to be responsible for the growth of the prostate gland. Many physicians answered the questionnaire affirmatively.

If the questioner's purpose was to determine his legal status in using a treatment, his research method was appropriate, to see whether the treatment seemed reasonable to others in the profession. Legally, a physician is safe if he can count on others to testify that his practice is standard. Unfortunately, for generations his study of the opinions of his peers became the "evidence" of the value of the estrogen treatment. Phrases such as "it is indicated," "treatment of choice," and "standard

> "...Simultaneous treatment of intact...rats with testosterone and estradiol-17β for 16 weeks consistently induced a putative precancerous lesion, termed dysplasia, in the dorsolateral prostate of all animals. Since treatment of rats with androgen alone did not elicit the same response, we concluded that estrogen played a critical role in the genesis of this proliferative lesion."[1]

practice" are used in medicine, as part of the pseudo-scientific mystique of the profession. Physicans who attempt to base their practice on methods that have a sound scientific basis are likely to find that they are violating the norms of their profession.

More than 25 years ago, when I started pointing out that deliberate misrepresentation had been involved in the continued designation of estrogen as "the female hormone," used as a basis for "hormone replacement therapies," I saw that it was hard for people to sustain a critical attitude toward language. Language is prior to judgment, law, science, reason. Those who define the terms set the rules.

By the mid-1980s, some studies had shown that estrogen treatment didn't prolong the survival of prostate cancer patients at all, but it was argued that the patients who received estrogen were happier than those who didn't.

Apparently, many physicians who were experts in conventional cancer treatment hadn't been impressed by the happiness of their patients who were receiving estrogen, because a survey at a conference of physicians found that many of them would choose to have no treatment if they learned they had prostate cancer. And more recently, there have been recommendations that older patients shouldn't be treated aggressively, because their cancers are usually so slow growing that they are likely to die of something else related to old age.

In spite of the articles I showed my friend, and my warning that estrogen can cause strokes and heart attacks, he decided to take the estrogen treatment. Within a few days he began suffering from asthma and disturbed sleep. Then he had a series of strokes and died.

Since it was known that estrogen treatment was dangerous for men, and that it increases blood clotting and vascular spasms, there had to be some overriding belief that led to its general use in treating prostate cancer. That belief seems to be that "estrogen, the female hormone, opposes testosterone, the male hormone, which is responsible for the growth—and therefore for the cancerization—of the prostate gland." Everything is wrong with that sentence, but you can find every part of the belief present and functioning in the medical literature. Just to give some context to the association of growth and cancerization, I should mention that Otto Warburg observed that all of the carcinogenic factors he studied caused tissue atrophy before cancer appeared. Another

important contextual point is that every hormone does many things, and every endocrine gland produces multiple hormones.

Since the time of Brown-Sequard and Eugen Steinach, it has been accepted that declining testicular function is a common feature of aging, and testosterone was probably the first hormone that was clearly found to decrease consistently with aging.[2,3]

It has seemed odd to many people that enlargement of the prostate should occur mainly in older men, if testosterone is the hormone that causes its growth, and estrogen is antagonistic to its growth. The nature of the growth of the old man's prostate is very different from its natural growth in youth.

It was also recognized decades ago that estrogen rises in men during old age,[4] as it rises in stress, disease, malnutrition, and hypothyroidism (which are also associated with old age). Estrogen is produced in fat[5,6] which tends to increase with age, when thyroid and progesterone are deficient. The conversion of testosterone to estrogen occurs in the testicle itself, but this conversion is also inhibited by the favorable hormonal environment of youth. The active thyroid hormone, T_3, declines with aging, and this necessarily lowers production of pregnenolone and progesterone. Increasingly, in both sexes, it appears that DHEA may rise during stress as a result of a deficiency of thyroid, progesterone, and pregnenolone.

In 1786, John Hunter reported that castration causes a decrease in the size of the prostate gland, and by the end of the 19th century castration was being advocated for treating enlargement of the prostate. In aging men, the prostate gland (both central and peripheral zones) atrophies, and it is within the atrophic gland that cancer cells can be found. Nodular, noncancerous enlargement may occur, with or without cancer. In 1935, an autopsy study showed carcinoma in the prostates of 30 % of men by the age of 50. Proliferation of ductal and epithelial tissue is closely associated with prostate cancer, a situation similar to that of the cancerous or precancerous breast.[7–9] The high probability of "epitheliosis" in association with cancer was seen in women in their early 40s, and in women over 60.[7] (Epitheliosis just refers to an exaggerated proliferation of epithelial cells, the cells covering all surfaces, including the lining of glands, and things as simple as irritation and vitamin A deficiency can cause these cells to proliferate.) In the breast, the proliferative epitheliosis is clearly caused by estrogenic stimulation. The

antagonism between estrogen and vitamin A in controlling epithelial proliferation (and possibly other cell types[10]) is clear wherever it has been tested; vitamin A restrains epithelial proliferation. (Wherever estrogen is a factor in the development of abnormal tissue, vitamin A supplementation would seem beneficial.)

In aging women and men, as the breasts and prostate atrophy, their estrogen/antiestrogen ratio increases.

In men with prostate cancer, the fluid secreted by the prostate contains significantly more estradiol than the fluid from men without cancer.[11] This is analogous to observations made in women with breast cancer.

The pituitary hormones have diverse functons, including effects on epithelial tissues, other than their "classical" functions. Growth hormone, ACTH,[12] and ACTH with prolactin[13] stimulate prostate growth. Prolactin—which is increased by estrogen—stimulates growth of the rat's lateral prostate,[14] and stimulates the growth of human prostate epithelial cells *in vitro*.[15] LH (luteinizing hormone) increases when progesterone or testosterone is deficient, and growth hormone and prolactin (which are closely associated in evolution) both increase under a variety of stressful situations, and with estrogenic stimulation. Prostate cancer patients who had higher levels of LH and lower testosterone died most quickly.[16] Also, a high ratio of testosterone to estradiol or of testosterone to prolactin corresponded to better survival[17] Considered separately, patients with higher testosterone levels had a better prognosis than those with lower levels, and patients with lower growth hormone levels did better than those with higher growth hormone levels.[18] Has anyone ever tried testosterone therapy for prostate cancer? Or, more practically, a generalized antiestrogenic therapy, using thyroid, progesterone, and pregnenolone? Other drugs (naloxone, bromocriptine, gonadotropin-releasing hormone agonists, and anti-growth hormone druges, e.g.) are available to regulate the pituitary hormones, and might be useful therapeutically or preventively.[19] Biskind and Biskind's work (1944) with ovarian tumors might be relevant to both testicular and prostate cancer.

Abnormal patterns of pituitary hormones reflect stress and hormonal imbalance, but they are also directly involved in widespread changes in tissue content of glycoproteins. The prostate is specialized to secrete large amounts of mucin. The endocrine physiology of prostate mucin

secretion is poorly understood, but it is likely that there are interactions between growth-regulatory and secretion-regulatory systems.

In recent years, prostate cancer has been one of the fastest increasing kinds of cancer, and it isn't apparent that increased treatment has had an effect in lowering the death rate. The postwar baby-boom (following the baby-bust of the great depression) created an abnormal age-structure of the population, that has been used to argue that the war against cancer is being won. Increasing environmental estrogens are known to cause many reproductive abnormalities, and their contribution to prostate cancer would get more attention if estrogen's role in prostate disease were better known. Environmental estrogens are clearly responsible for genital deformities and sterility in many species of wild animals, but when the causal link is made between estrogens and human abnormalities, the estrogen industry sends its shills in to create controversy and confusion. Even the effects of estrogens in sewage, known for decades, are treated as State Secrets: "There had been reports of hermaphroditic fishes in one or two rivers, and government investigators had been studying them since the late 1970s. But no one had been aware of the work because it was classified."[20]

Testicular cancer is easy to diagnose, and its incidence has clearly increased (100 % in white men, 200 % in black men) since 1950. Undescended testicles, urethral abnormalities, etc., similar to those seen in DES sons and in wild animals, have also increased. So the tremendous increase in the death rate from prostate cancer during the same time has a meaningful context.

Although the animal studies showed that estrogen treatment promotes enlargement of the prostate, it was possible to suppose that the human prostate's growth might be stimulated only by testosterone, until tests were done *in vitro* to determine the effects of hormones on cell division.

In human prostate slices, several hormones (including insulin, and probably prolactin) stimulated cell division; testosterone did not, under these experimental conditions.[21] Contrary to the stereotyped ideas, there are suggestions that supplementary androgens could control prostate cancer,[22] and that antagonists to prolactin and estrogen might be appropriately used in hormonal therapy.[23,24]

By the age of 50, men often show an excess of both prolactin and estrogen, and a deficiency of thyroid and testosterone. This is the age at which enlargement of the prostate often becomes noticeable.

Estrogen's role in prostate growth and cancerization is clear: "...simultaneous treatment of intact...rats with testosterone and estradiol-17beta for 16 weeks consistently induced a putative precancerous lesion, termed dysplasia, in the dorsolateral prostate of all animals. Since treatment of rats with androgen alone did not elicit the same response, we concluded that estrogen played a critical role in the genesis of this proliferative lesion."[1]

Progesterone and pregnenolone also decline in aging men. Several studies using synthetic progestins have shown that they effectively shrink the hypertrophic prostate, and the saw palmetto remedy for prostate enlargement has been reported to contain pregnenolone, or something similar to it. These materials might be expected to reduce conversion of testosterone or other androgens to estrogen.

The prostaglandins were discovered in prostatic fluid, where they occur in significant concentrations. They are so deeply involved with the development of cancers of all sorts that aspirin and other prostaglandin inhibitors should be considered as a basic part of cancer therapy. The prostaglandins have local and systemic effects that promote cancer growth. ("The prostaglandins and related eicosanoids synthesized from polyunsaturated fatty acid precursors have been implicated as modulators of tumor metastasis, host immunoregulation, tumor promotion, and cell proliferation."[25])

Estrogens cause elevation of free fatty acids, and there are many interactions between the unsaturated fatty acids and estrogen, including their metabolism to prostaglandins, and their peroxidation. Estrogen's roles as free-radical promoter, DNA toxin, carcinogen, tumor promotor, modifier of tissue growth factors, anti-thymic hormone, etc., as well as its local effects on the prostate gland, have to be kept in mind. Most of the interest in studying estrogen's contributions to prostate cancer relates to the existence of estrogen receptors in various parts of the prostate. While that is interesting, it tends to distract attention from the fact that many of estrogen's most important actions don't involve the "receptors." A direct excitatory action on prostate cells, and indirect actions by way of the pituitary, pancreas, thyroid, adrenal, fatty acids,

prostaglandins, histamine and circulation are probably essential parts of the cancerization process.

The unsaturated fatty acids, but not the saturated fatty acids, free estrogen from the serum proteins that bind it, and increase its availability and activity in tissue cells.

Thyroid supplementation, adequate animal protein, trace minerals, and vitamin A are the first things to consider in the prevention of prostate hypertrophy and cancer. Nutritional and endocrine support can be combined with rational anticancer treatments, since there is really no sharp line between different approaches that are aimed at achieving endocrine and immunological balance, without harming anything.

Avoiding tissue atrophy is very closely related to promoting healthy regeneration. These processes require efficient energy production, and an appropriate balance between stimulation and resources. Growth hormone is sometimes recommend to correct tissue atrophy, but the evidence seems reasonably clear that it is a factor in the promotion of tumefaction of the prostate. The only study I have seen suggesting that it might be beneficial in prostatic cancer was a 14 day experiment done in female rats. Numerous publications suggest that blocking growth hormone is beneficial in treating prostate cancer; in future newsletters I will be discussing the evidence that growth hormone, like estrogen, cortisol, and unsaturated fats, tends to promote degenerative changes of aging.

Protective CO_2 and Aging

Ray Peat's Newsletter, 2011

THE therapeutic effects of increasing carbon dioxide are being more widely recognized in recent years. Even Jane Brody, the NY Times writer on health topics, has favorably mentioned the use of the Buteyko method for asthma, and the idea of "permissive hypercapnia" during mechanical ventilation, to prevent lung damage from excess oxygen, has been discussed in medical journals. But still very few biologists recognize its role as a fundamental, universal protective factor. I think it will be helpful to consider some of the ways carbon dioxide might be controlling situations that otherwise are poorly understood.

The brain has a high rate of oxidative metabolism, and so it forms a very large proportion of the carbon dioxide produced by an organism. It also governs, to a great extent, the metabolism of other tissues, including their consumption of oxygen and production of carbon dioxide or lactic acid. Within a particular species, the rate of oxygen consumption increases in proportion to brain size, rather than body weight. Between very different species, the role of the brain in metabolism is even more obvious, since the resting metabolic rate corresponds to the size of the brain. For example, a cat's brain is about the size of a crocodile's, and their oxygen consumption at rest is similar, despite their tremendous difference in body size.

Stress has to be understood as a process that develops in time, and the brain (especially the neocortex and the frontal lobes) organizes the adaptive and developmental processes in both the spatial and temporal dimensions. The meaning of a situation influences the way the organism responds. For example, the stress of being restrained for a long time can cause major gastrointestinal bleeding and ulcerization, but if the animal has the opportunity to bite something during the stress (signifying its ability to fight back, and the possibility of escape) it can avoid the stress ulcers.

The patterning of the nervous activity throughout the body governs the local ability to produce carbon dioxide. When the cortex of the brain is damaged or removed, an animal becomes rigid, so the cortex is considered to have a "tonic inhibitory action" on the body. But when the nerves are removed from a muscle (for example, by disease or accident),

the muscle goes into a state of constant activity, and its ability to oxidize glucose and produce carbon dioxide is reduced, while its oxidation of fatty acids persists, increasing the production of toxic oxidative fragments of the fatty acids, which contributes to the muscle's atrophy.

The organism's intentions, expectations, or plans, are represented in the nervous system as a greater readiness for action, and in the organs and tissues controlled by the nerves, as an increase or decrease of oxidative efficiency, analogous to the differences between innervated and denervated muscles. This pattern in the nervous system has been called "the acceptor of action," because it is continually being compared with the actual situation, and being refined as the situation is evaluated. The state of the organism, under the influence of a particular acceptor of action, is called a "functional system," including all the components of the organism that participate most directly in realizing the intended adaptive action.

The actions of nerves can be considered anabolic, because during a stressful situation in which the catabolic hormones of adaption, e.g., cortisol, increase, the tissues of the functional system are protected, and while idle tissues may undergo autophagy or other form of involution, the needs of the active tissues are supplied with nutrients from their breakdown, allowing them to change and, when necessary, grow in size or complexity.

The brain's role in protecting against injury by stress, when it sees a course of action, has a parallel in the differences between concentric (positive, muscle shortening) and eccentric (negative, lengthening under tension) exercise, and also with the differences between innervated and denervated muscles. In eccentric exercise and denervation, less oxygen is used and less carbon dioxide is produced, while lactic acid increases, displacing carbon dioxide, and more fat is oxidized. Prolonged stress similarly decreases carbon dioxide and increases lactate, while increasing the use of fat.

Darkness is stressful and catabolic. For example, in aging people, the morning urine contains nearly all of the calcium lost during the 24 hour period, and mitochondria are especially sensitive to the destructive effects of darkness. Sleep reduces the destructive catabolic effects of darkness. During the rapid-eye-movement (dreaming) phase of sleep, breathing is inhibited, and the level of carbon dioxide in the tissues accumulates. In restful sleep, the oxygen tension is frequently low

enough, and the carbon dioxide tension high enough, to trigger the multiplication of stem cells and mitochondria.

Dreams represent the "acceptor of action" operating independently of the sensory information that it normally interacts with. During dreams, the brain (using a system called the Ascending Reticular Activating System) disconnects itself from the sensory systems. I think this is the nervous equivalent of concentric/positive muscle activity, in the sense that the brain is in control of its actions. The active, dreaming phase of sleep occurs more frequently in the later part of the night, as morning approaches. This is the more stressful part of the night, with cortisol and some other stress hormones reaching a peak at dawn, so it would be reasonable for the brain's defensive processes to be most active at that time. The dreaming process in the brain is associated with deep muscle relaxation, which is probably associated with the trophic (restorative) actions of the nerves.

In ancient China the Taoists were concerned with longevity, and according to Joseph Needham (*Science and Civilization in China*) their methods included the use of herbs, minerals, and steroids extracted from the urine of children. Some of those who claimed extreme longevity practiced controlled breathing and tai chi (involving imagery, movement, and breathing), typically in the early morning hours, when stress reduction is most important. As far as I know, there are no studies of carbon dioxide levels in practitioners of tai chi, but the sensation of warmth they typically report suggests that it involves hypoventilation.

In the 1960s, a Russian researcher examined hospital records of measurements of newborn babies, and found that for several decades the size of their heads had been increasing. He suggested that it might be the result of increasing atmospheric carbon dioxide.

The experiences and nutrition of a pregnant animal are known to affect the expression of genes in the offspring, affecting such things as allergies, metabolic rate, brain size, and intelligence. Miles Storfer[1] has reviewed the evidence for epigenetic environmental control of brain size and intelligence. The main mechanisms of epigenetic effects or "imprinting" are now known to involve methylation and acetylation of the chromosomes (DNA and histones).

Certain kinds of behavior, as well as nutrition and other environmental factors, increase the production and retention of carbon dioxide. The normal intrauterine level of carbon dioxide is high, and it can be

increased or decreased by changes in the mother's physiology. The effects of carbon dioxide on many biological processes involving methylation and acetylation of the genetic material suggest that the concentration of carbon dioxide during gestation might regulate the degree to which parental imprinting will persist in the developing fetus. There is some evidence of increased demethylation associated with the low level of oxygen in the uterus.[2] A high metabolic rate and production of carbon dioxide would increase the adaptability of the new organism, by decreasing the limiting genetic imprints.

A quick reduction of carbon dioxide caused by hyperventilation can provoke an epileptic seizure, and can increase muscle spasms and vascular leakiness, and (by releasing serotonin and histamine) contribute to inflammation and clotting disorders. On a slightly longer time scale, a reduction of carbon dioxide can increase the production of lactic acid, which is a promoter of inflammation and fibrosis. A prolonged decrease in carbon dioxide can increase the susceptibility of proteins to glycation (the addition of aldehydes, from polyunsaturated fat peroxidation or methylglyoxal from lactate metabolism, to amino groups), and a similar process is likely to contribute to the methylation of histones, a process that increases with aging. Histones regulate genetic activity.

With aging, DNA methylation is increased.[3] I suggest that methylation stabilizes and protects cells when growth and regeneration aren't possible (and that it's likely to increase when CO_2 isn't available). Hibernation[4] and sporulation[5,6] appear to use methylation protectively.

Parental stress, prenatal stress, early life stress, and even stress in adulthood contribute to "imprinting of the genes," partly through methylation of DNA and the histones.

Methionine and choline are the main dietary sources of methyl donors. Restriction of methionine has many protective effects, including increased average (42%) and maximum (44%) longevity in rats.[7] Restriction of methyl donors causes demethylation of DNA.[8] The age accelerating effect of methionine might be related to disturbing the methylation balance, inappropriately suppressing cellular activity. Besides its effect on the methyl pool, methionine inhibits thyroid function and damages mitochondria.

The local concentration of carbon dioxide in specific tissues and organs can be adjusted by nervous and hormonal activation or inhibition of the carbonic anhydrase enzymes, that accelerate the conversion of

CO_2 to carbonic acid, H_2CO_3. The activity of carbonic anhydrase can determine the density and strength of the skeleton, the excitability of nerves, the accumulation of water, and can regulate the structure and function of the tissues and organs.

Ordinarily, carbon dioxide and bicarbonate are thought of only in relation to the regulation of pH, and only in a very general way. Because of the importance of keeping the pH of the blood within a narrow range, carbon dioxide is commonly thought of as a toxin, because an excess can cause unconsciousness and acidosis. But increasing carbon dioxide doesn't necessarily cause acidosis, and acidosis caused by carbon dioxide isn't as harmful as lactic acidosis.

Frogs and toads, being amphibians, are especially dependent on water, and in deserts or areas with a dry season they can survive a prolonged dry period by burrowing into mud or sand. Since they may be buried 10 or 11 inches below the surface, they are rarely found, and so haven't been extensively studied. In species that live in the California desert, they have been known to survive 5 years of burial without rainfall, despite a moderately warm average temperature of their surroundings. One of their known adaptations is to produce a high level of urea, allowing them to osmotically absorb and retain water. (Very old people sometimes have extremely high urea and osmotic tension.)

Some laboratory studies show that as a toad burrows into mud, the amount of carbon dioxide in its tissues increases. Their skin normally functions like a lung, exchanging oxygen for carbon dioxide. If the toad's nostrils are at the surface of the mud, as dormancy begins its breathing will gradually slow, increasing the carbon dioxide even more. Despite the increasing carbon dioxide, the pH is kept stable by an increase of bicarbonate.[9] A similar increase of bicarbonate has been observed in hibernating hamsters and doormice.

Thinking about the long dormancy of frogs reminded me of a newspaper story I read in the 1950s. Workers breaking up an old concrete structure found a dormant toad enclosed in the concrete, and it revived soon after being released. The concrete had been poured decades earlier.

Although systematic study of frogs or toads during their natural buried estivation has been very limited, there have been many reports of accidental discoveries that suggest that the dormant state might be extended indefinitely if conditions are favorable. Carbon dioxide has antioxidant effects, and many other stabilizing actions, including protec-

tion against hypoxia and the excitatory effects of intracellular calcium and inflammation.[10–15]

When mitochondria are "uncoupled," they produce more carbon dioxide than normal, and the mitochondria produce fewer free radicals. Animals with uncoupled mitochondria live longer than animals with the ordinary, more efficient mitochondria, that produce more reactive oxidative fragments. One effect of the high rate of oxidation of the uncoupled mitochondria is that they can eliminate polyunsatured fatty acids that might otherwise be integrated into tissue structures, or function as inappropriate regulatory signals.

Birds have a higher metabolic rate than mammals of the same size, and live longer. Their tissues contain fewer of the highly unsaturated fatty acids. Queen bees, which live many times longer than worker bees, have mainly monounsaturated fats in their tissues, while the tissues of the short-lived worker bees, receiving a different diet, within a couple of weeks of hatching will contain highly unsaturated fats.

Bats have a very high metabolic rate, and an extremely long lifespan for an animal of their size. While most animals of their small size live only a few years, many bats live a few decades. Bat caves usually have slightly more carbon dioxide than the outside atmosphere, but they usually contain a large amount of ammonia, and bats maintain a high serum level of carbon dioxide, which protects them from the otherwise toxic effects of the ammonia.

The naked mole rat, another small animal with an extremely long lifespan (in captivity they have lived up to 30 years, 9 or 10 times longer than mice of the same size) has a low basal metabolic rate, but I think measurements made in laboratories might not represent their metabolic rate in their natural habitat. They live in burrows that are kept closed, so the percentage of oxygen is lower than in the outside air, and the percentage of carbon dioxide ranges from 0.2 % to 5 % (atmospheric CO_2 is about 0.038). The temperature and humidity in their burrows can be extremely high, and to be very meaningful their metabolic rate would have to be measured when their body temperature is raised by the heat in the burrow.

When they have been studied in Europe and the U.S., there has been no investigation of the effect of altitude on their metabolism, and these animals are native to the high plains of Kenya and Ethiopia, where the low atmospheric pressure would be likely to increase the level of carbon

dioxide in their tissues. Consequently, I doubt that the longevity seen in laboratory situations accurately reflects the longevity of the animals in their normal habitat.

Besides living in a closed space with a high carbon dioxide content, mole rats have another similarity to bees. In each colony, there is only one female that reproduces, the queen, and, like a queen bee, she is the largest individual in the colony. In beehives, the workers carefully regulate the carbon dioxide concentration, which varies from about 0.2 % to 6 %, similar to that of the mole rat colony. A high carbon dioxide content activates the ovaries of a queen bee, increasing her fertility.

Since queen bees and mole rats live in the dark, I think their high carbon dioxide compensates for the lack of light. (Both light and CO_2 help to maintain oxidative metabolism and inhibit lactic acid formation.) Mole rats are believed to sleep very little. During the night, normal people tolerate more CO_2, and so breathe less, especially near morning, with increased active dreaming sleep.

A mole rat has never been known to develop cancer. Their serum C-reactive protein is extremely low, indicating that they are resistant to inflammation. In humans and other animals that are susceptible to cancer, one of the genes that is likely to be silenced by stress, aging, and methylation is p53, a tumor-suppressor gene.

If the intrauterine experience, with low oxygen and high carbon dioxide, serves to "reprogram" cells to remove the accumulated effects of age and stress, and so to maximize the developmental potential of the new organism, a life that's lived with nearly those levels of oxygen and carbon dioxide might be able to avoid the progressive silencing of genes and loss of function that cause aging and degenerative diseases.

Several diseases and syndromes are now thought to involve abnormal methylation of genes. Prader-Willi sydrome, Angelman's syndrome, and various "autistic spectrum disorders," as well as post-traumatic stress disorder and several kinds of cancer seem to involve excess methylation.

Moderate methionine restriction (for example, using gelatin regularly in the diet) might be practical, but if increased carbon dioxide can activate the demethylase enzymes in a controlled way, it might be a useful treatment for the degenerative diseases and for aging itself.

The low carbon dioxide production of hypothyroidism,[16] and the respiratory alkalosis of estrogen excess, are often overlooked. An adequate

supply of calcium, and sometimes supplementation of salt and baking soda, can increase the tissue content of CO_2.

RU486, Cancer, Estrogen, and Progesterone

Ray Peat's Newsletter, 2007

RECENTLY many people have been disturbed by reading claims that progesterone can cause cancer, or diabetes, or autoimmune diseases, or heart disease, or Alzheimer's disease. A flurry of press conferences, and a few groups of "molecular biologists" working on "progesterone receptors," and the results of studies in which Prempro (containing a synthetic "progestin") increased breast cancer, have created great confusion and concern, at least in the English speaking countries.

Wyeth, the manufacturer of Prempro, has been highly motivated to recover their sales and profits that declined about 70 % in the first two years after the Women's Health Initiative announced its results. When billions of dollars in profits are involved, clever public relations can achieve marvelous things.

Women and other mammals that are deficient in progesterone, and/or that have an excess of estrogen, have a higher than average incidence of cancer. Animal experiments have shown that administering progesterone could prevent cancer. Cells in the most cancer-susceptible tissues proliferate in proportion to the ratio of estrogen to progesterone. When the estrogen dominance persists for a long time without interruption, there are progressive distortions in the structure of the responsive organs—the uterus, breast, pituitary, lung, liver, kidney, brain, and other organs—and those structural distortions tend to progress gradually from fibroses to cancer.

As a result of the early studies in both humans and animals, progesterone was used by many physicians to treat the types of cancer that were clearly caused by estrogen, especially uterine, breast, and kidney cancers. But by the 1950s, the drug industry had created the myth that their patented synthetic analogs of progesterone were medically more effective than progesterone itself, and the result has been that medroxyprogesterone acetate and other synthetics have been widely used to treat women's cancers, including breast cancer.

Unfortunately, those synthetic compounds have a variety of functions unlike progesterone, including some estrogenic and/or androgenic and/or glucocorticoid and/or antiprogesterone functions, besides other special, idiosyncratic side effects. The rationale for their use was that

they were "like progesterone, only better." The unpleasant and unwanted truth is that, as a group, they are seriously carcinogenic, besides being toxic in a variety of other ways. Thousands of researchers have drawn conclusions about the effects of progesterone on the basis of their experiments with a synthetic progestin.

The earliest studies of estrogen and progesterone in the 1930s had the great advantage of a scientific culture that was relatively unpolluted by the pharmaceutical industry. As described by Carla Rothenberg, the massive manipulation of the medical, regulatory, and scientific culture by the estrogen industry began in 1941. After that, the role of metaphysics, word magic, and epicycle-like models increasingly replaced empirical science in endocrinology and cell physiology.

As the estrogen industry began losing billions of dollars a year following the 2002 report from the Women's Health Initiative regarding estrogen's toxicity, and as it was noticed that progesterone sales had increased more than 100-fold, it was clear what had to be done—the toxic effects of estrogen had to be transferred to progesterone. For more than 50 years, progesterone was recognized to be antimitotic and anti-inflammatory and anticarcinogenic, but suddenly it has become a mitogenic pro-inflammatory carcinogen.

Science used to involve confirmation or refutation of published results and conclusions. A different experimenter, using the technique described in a publication, would often get a different result, and a dialog or disputation would develop, sometimes continuing for years, before consensus was achieved, though many times there would be no clear conclusion or consensus.

In that traditional scientific environment, it was customary to recognize that a certain position remained hypothetical and controversial until some new technique or insight settled the question with some degree of clarity and decisiveness. People who cherry-picked studies to support their position, while ignoring contradictory evidence, were violating the basic scientific principles of tentativeness and reasonableness. Contradictory, as well as confirmatory, data have to be considered.

But when a single experiment involves several people working for a year or more, at a cost of a million or more dollars, who is going to finance an experiment that "would merely confirm" those results? The newly developed techniques for identifying specific molecules are often very elaborate and expensive, and as a result only a few kinds of molecule

are usually investigated in each experiment. The results are open to various interpretations, and most of those interpretations depend on results from other studies, whose techniques, results, and conclusions have never been challenged, either. There is no significant source of funding to challenge the programs of the pharmaceutical industry.

The result is that the pronouncements of the principal investigator, and the repetitions of those conclusions in the mass media, create a culture of opinion, without the foundation of multiple confirmations that used to be part of the scientific process. The process has taken on many of the features of a cult, in which received opinions are repeatedly reinforced by the investment of money and authority. Newspaper reporters know that the team of investigators spent two years on their project, and the lead investigator wears a white lab coat during the interview, so the reporters don't notice that the investigators' conclusion is a non sequitur, supported by chains of non sequiturs.

The public gets most of its information about science from the mass media, and the increasingly concentrated ownership of the media contributes to the use of scientific news as an adjunct to their main business, advertising and product promotion. The pharmaceutical industry spends billions of dollars annually on direct-to-consumer advertising, so the big scientific news, for the media, is likely to be anything that will increase their advertising revenue.

Social-economic cults often simplify the thought processes required by the participants, by inventing a scapegoat. The estrogen cult has decided that progesterone will be its scapegoat.

Hans Selye argued that steroid hormones should be named by their origin, or by their chemical structural names, rather than their effects, because each hormone has innumerable effects. To name a substance according to its effects is to predict and to foreordain the discoveries that will be made regarding its effects.

The common system of hormonal names according to their putative effects has allowed ideology and metaphysical ideas to dominate endocrinology. The worst example of metaphysical medicine was the use, for more than 50 years, of "estrogen, the female hormone" to treat prostate cancer, in the belief that "male hormones" cause the cancer, and that the female hormone would negate it. This word magic led to a vast psychotic medical endeavor, that has only recently been reconsidered.

Within the scheme of hormones understood according to their names, "hormone receptors" were proposed to be the mechanism by which hormones produced their effects. Each hormone had a receptor. If another substance bound more strongly than the hormone to its receptor, without producing the effects of the hormone, it was called an antihormone.

The industry of synthetic hormones used the ideology of unitary hormonal action to identify new substances as pharmaceutical hormones, that were always in some way said to be better than the natural hormones—for example by being "orally active," unlike natural hormones, supposedly. Physicians docilely went along with whatever the drug salesmen told them. If a drug was classified as a "progestin" by a single reaction in one animal tissue, then it had a metaphysical identity with the natural hormone, except that it was better, and patentable.

The natural hormones eventually were assigned any of the toxic properties that were observed for the pharmaceutical products "in their class." If synthetic progestins caused heart disease, birth defects, and cancer, then the "natural progestin" was assumed to do that, too. It's important to realize the impact of logical fallacies on the medical culture.

Like the hormones themselves, which metaphysically supposedly acted upon one receptor, to activate one gene (or set of genes), the antihormones came to be stereotyped. If a particular hormonal action was blocked by a chemical, then that substance became an antagonistic antihormone, and when its administration produced an effect, that effect was taken to be the result of blocking the hormone for which it was "the antagonist."

The "antiprogesterone" molecule, RU486, besides having some progesterone-like and antiestrogenic properties, also has some androgenic,[1] antiandrogenic, and antiglucocorticoid properties. Experiments in which it is used might have pharmaceutical meaning, but they so far have very little clear biological meaning.

Adding to the conceptual sloppiness of the "molecular biology" wing of endocrinology, the culture in which pharmaceutical products had come to dominate medical ideas about hormones allowed the conventional pharmaceutical vehicles to be disregarded in most experiments, both in vitro and *in vivo*. If progesterone was injected into patients mixed with sesame oil and benzyl alcohol, then it often didn't occur to animal experimenters to give control injections of the solvent. For

in vitro studies, in a watery medium, oil wouldn't do, so they would use an alcohol solvent, and again often forgot to do a solvent control experiment.

The importance of the solvent was seen by an experimenter studying the effect of vitamin E on age pigment in nerves. It occurred to that experimenter to test the ethyl alcohol alone, and he found that it produced almost the same effect as that produced by the solution of alcohol and vitamin E. Workers with hormones often just assume that a little alcohol wouldn't affect their system. But when the effects of alcohol by itself have been studied, many of the effects produced by very low concentrations happen to be the same effects that have been ascribed to hormones, such as progesterone.

In some cases, the solvent allows the hormone to crystallize, especially if the solvent is water-miscible, and fails to distribute it evenly through the medium and cells as the experimenter assumed would happen, and so the experimenter reports that the hormone is not effective in that kind of cell, even though the hormone didn't reach the cells in the amount intended.

These are four of the common sources of error about progesterone: (1) Saying that progesterone has produced an effect which was produced by a different substance. (2) Saying that progesterone is the cause of a certain effect, if an "anti-progesterone" chemical prevents that effect. (3) Saying that progesterone caused something, when in fact the solvent caused it. And (4) saying that progesterone fails to do something, when progesterone hasn't been delivered to the system being studied.

Many years ago, experimenters who wanted to minimize the problems involved in administering progesterone in toxic solvents found that, with careful effort, progesterone could be transferred to a protein, such as albumin, and that the albumin-progesterone complex could be washed to remove the solvent. In this form, the progesterone can be delivered to cells in a form that isn't radically different from the form in which it naturally circulates in the body. Apparently, the labor involved discourages the widespread use of this technique.

Although the industry's early generalizations about estrogen and progesterone, defining them as "the female hormone" and "the pregnancy hormone," were radically mistaken, some useful generalizations about their effects were gradually being built up during the first few decades in which their chemical and physiological properties were studied.

Estrogen's name, derived from the gadfly, accurately suggests its role as an excitant, getting things started. Progesterone's name, relating to pregnancy, is compatible with thinking of it as an agent of calming and fulfillment. But these properties show up in every aspect of physiology, and the special cases of female estrus and pregnancy can be properly understood only in the larger context, in which, for example, progesterone is a brain hormone in both sexes and at all ages, and estrogen is an essential male hormone involved in the sperm cell's function and male libido.

Progesterone can, without estrogen, create the uterine conditions for implantation of an embryo,[2,3] and it has many other features that can be considered apart from estrogen, such as its regulation of salts, energy metabolism, protein metabolism, immunity, stress, and inflammation, but without understanding its opposition to estrogen, there will be no coherent understanding of progesterone's biological meaning.

Both estrogen and progesterone are hydrophobic molecules (progesterone much more so than estrogen) which bind with some affinity to many components of cells. Certain proteins that strongly bind the hormones are called their receptors.

Cells respond to stimulation by estrogen by producing a variety of molecules, including the "progesterone receptor" protein. When progesterone enters the cell, binding to these proteins, the estrogenic stimulation is halted, by a series of reactions in which the estrogen receptors disintegrate, and in which estrogen is made water soluble by the activation of enzymes that attach sulfate or a sugar acid, causing it leave the cell and move into the bloodstream, and by reactions that prevent its reentry into the cell by inactivating another type of enzyme, and that suppress its *de novo* formation in the cell, and that oxidize it into a less active form. Progesterone terminates estrogen's cellular functions with extreme thoroughness.

A recent publication in Science ("Prevention of Brca1-mediated mammary tumorigenesis in mice by a progesterone antagonist," Poole, et al., Dec. 1, 2006), with associated press conferences, reported an experiment in which a special kind of mouse was prepared, which lacked two tumor-suppressing genes called BRCA and p53.

One of the functions of the BRCA gene product is to repair genetic damage, and another function is to (like progesterone) suppress the estrogen receptor and its functions. Estrogen, and some environmental

carcinogens, can suppress the BRCA gene product. Estrogen can also turn off the tumor suppressor protein, p53. So it is interesting that a group of experimenters chose to produce a mouse that lacked both the normal BRCA and p53 genes. They had a mouse that was designed to unleash estrogen's effects, and that modeled some of the features of estrogen toxicity and progesterone deficiency.

This mouse, lacking an essential gene that would allow progesterone to function normally, probably affecting progesterone's ability to eliminate the estrogen receptor, also lacked the tumor suppressor gene p53, which is required for luteinization;[4] in its absence, progesterone synthesis is decreased, estrogen synthesis is increased.

(Chen, Y, et al., 1999: BRCA represses the actions of estrogen and its receptor, and, like progesterone, activates the p21 promoter, which inhibits cell proliferation. Aspirin and vitamin D also act through p21.)

The mutant BRCA gene prevents the cell, even in the presence of progesterone, from turning off estrogen's effects the way it should. The antiestrogenic RU486 (some articles below), which has some of progesterone's effects (including therapeutic actions against endometrial and breast cancer), appears to overcome some of the effects of that mutation.

It might have been proper to describe the engineered mouse that lacked both the BRCA and the p53 genes as a mouse in which the effects of estrogen excess and progesterone deficiency would be especially pronounced and deadly. To speak of progesterone as contributing to the development of cancer in that specially designed mouse goes far beyond bad science. However, that study makes sense if it is seen as preparation for the promotion of a new drug similar in effect to RU486, to prevent breast cancer.

The study's lead author, Eva Lee, quoted by a university publicist, said "We found that progesterone plays a role in the development of breast cancer by encouraging the proliferation of mammary cells that carry a breast cancer gene." But they didn't measure the amount of progesterone present in the animals. They didn't "find" anything at all about progesterone. The "anti-progesterone" drug they used has been used for many years to treat uterine, ovarian, and breast cancers, in some cases with progesterone, to intensify its effects, and its protective effects are very likely the result of its antiestrogenic and anti-cortisol effects, both of which are well established, and relevant. In some cases, it acts like progesterone, only more strongly.

"Other more specific progesterone blockers are under development," Lee notes. And the article in Science magazine looks like nothing more than the first advertisement for one that her husband, Wen-Hwa Lee, has designed.

According to publicists at the University of California, Irvine, "Lee plans to focus his research on developing new compounds that will disrupt end-stage cancer cells. The goal is a small molecule that, when injected into the blood stream, will act as something of a biological cruise missile to target, shock and awe the cancerous cells." "In this research, he will make valuable use of a breast cancer model developed by his wife." "She developed the model, and I will develop the molecule," Lee says. "We can use this model to test a new drug and how it works in combination with old drugs."

"Previously we blamed everything," Lee says of his eye cancer discovery. "We blamed electricity, we blamed too much sausage—but in this case it's clear: It's the gene's fault."

The things that these people know, demonstrated by previous publications, but that they don't say in the Science article, are very revealing. The retinoblastoma gene (and its protein product), a specialty of Wen-Hwa Lee, is widely known to be a factor in breast cancer, and to be responsive to progesterone, RU486, and p21. Its links to ubiquitin, the hormone receptors, proteasomes, and the BRCA gene are well known, but previously they were seen as linking estrogen to cell proliferation, and progesterone to the inhibition of cellular proliferation.

By organizing their claims around the idea that RU486 is acting as an antiprogesterone, rather than as a progesterone synergist in opposing estrogen, Eva Lee's team has misused words to argue that it is progesterone, rather than estrogen, that causes breast cancer. Of the many relevant issues that their publication ignores, the absence of measurements of the actual estrogen and progesterone in the animals' serum most strongly suggests that the project was not designed for proper scientific purposes.

They chose to use techniques that are perfectly inappropriate for showing what they claim to show.

In the second paragraph of their article, Poole, et al., say "Hormone replacement therapy with progesterone and estrogen, but not estrogen alone, has been associated with an elevation risk in postmenopausal women." Aside from the gross inaccuracy of saying "progesterone," rather than synthetic progestin, they phrase their comment about "es-

trogen alone" in a way that suggests an identity of purpose with the estrogen industry apologists, who have been manipulating the data from the WHI estrogen-only study, clearly to lay the blame on progesterone. (Women who took estrogen had many more surgeries to remove mammographically abnormal breast tissue. This would easily account for fewer minor cancer diagnoses; despite this, there were more advanced cancers in the estrogen group.)

While the Poole, et al., group are operating within a context of new views regarding estrogen, progesterone, and cancer, they are ignoring the greater part of contemporary thinking about cancer, a consensus that has been growing for over 70 years: All of the factors that produce cancer, including breast cancer, produce inflammation and cellular excitation.

Progesterone is antiinflammatory, and reduces cellular excitation.

Even within their small world of molecular endocrinology, thinking in ways that have been fostered by computer technology, about gene networks, interacting nodes, and crosstalk between pathways, their model and their arguments don't work. They have left out the complexity that could give their argument some weight.

The medical mainstream has recognized for 30 years that progesterone protects the uterus against cancer; that was the reason for adding Provera to the standard menopausal hormonal treatment. The new claim that natural progesterone causes breast cancer should oblige them to explain why the hormone would have opposite effects in different organs, but the mechanisms of action of estrogen and progesterone are remarkably similar in both organs, even when examined at the molecular level. If "molecular endocrinologists" are going to have interpretations diametrically opposed to classical endocrinology (if black is to be white, if apples are to fall up), they will have to produce some very interesting evidence.

Cancer is a malignant (destructive, invasive) tumor that kills the organism. The main dogma regarding its nature and origin is that it differs genetically from the host, as a result of mutations. Estrogen causes mutations and other forms of genetic instability, as well as cancer itself. Progesterone doesn't harm genes or cause genetic instability.

The speculative anti-progesterone school has put great emphasis on the issue of cellular proliferation, with the reasoning that proliferating cells are more likely to undergo genetic changes. And synthetic progestins often do imitate estrogen and increase cellular proliferation.

People like the Lees are asserting as an established fact that progesterone increases cellular proliferation.

A paper by Soderqvist has been cited as proof that progesterone increases the proliferation of breast cells. He saw more mitoses in the breasts during the luteal phase of the menstrual cycle, and said the slightly increased mitotic rate was "associated with" progesterone. Of course, estrogen increased at the same time, and estrogen causes sustained proliferation of breast cells, while progesterone stimulation causes only two cell divisions, ending with the differentiation of the cell.[5]

One of the ways that progesterone stops proliferation and promotes differentiation is by keeping the retinoblastoma protein in its unphosphorylated, active protective state[6] The effects of estrogen and progesterone on that protein are reciprocal.[7] It's hard for me to imagine that the Lees don't know about these hormonal effects on Wen-Hwa's retinoblastoma gene product.

The inactivation of that protein by hyperphosphorylation is part of a general biological process, in which activation of a cell (by injury or nervous or hormonal or other stimulation, including radiation) leads to the activation of a large group of about 500 enzymes, phosphorylases, which amplify the stimulation, and cause the cell to respond by becoming active in many ways, for example, by stopping the synthesis of glycogen, and beginning its conversion to glucose to provide energy for the adaptive responses, that include the activation of genes and the synthesis or destruction of proteins. Another set of enzymes, the phosphatases, remove the activating phosphate groups, and allow the cell to return to its resting state.

The "molecular" endocrinologists and geneticists are committed to a reductionist view of life, the view that DNA is the essence, the secret, of life, and that it controls cells through its interactions with smaller molecules, such as the hormone receptors.

The idea of hormone receptors can be traced directly to the work of Elwood Jensen, who started his career working in chemical warfare, at the University of Chicago. Jensen claims that an experiment he did in the 1950s "caused the demise" of the enzymic-redox theory of estrogen's action, by showing that uterine tissue can't oxidize estradiol, and that its only action is on the genes, by way of "the estrogen receptor." But the uterus and other tissues do oxidize estradiol, and its cyclic oxidation and

reduction is clearly involved in some of estrogen's toxic and excitatory effects.

For some reason, the military is still interested in hormone receptors. Lawrence National Weapons Laboratory (with its giant "predictive science" computer) is now the site of some of the anti-progesterone research.

Molecular biologists have outlined a chain of reactions, starting at the cell surface, and cascading through a series of phosphorylations, until the genes are activated. The cell surface is important, because cells are always in contact with something, and their functions and structure must be appropriate for their location. But the reductionist view of a network of phosphorylating enzymes ignores some facts.

Glycogen phosphorylase was the first enzyme whose activity was shown to be regulated by structural changes, allosterism. The active form is stabilized by phosphorylation, but this process takes seconds or minutes to develop, and the enzyme becomes active immediately when the cell is stimulated, for example in muscle contraction, within milliseconds. This kind of allosteric activation (or inactivation) can be seen in a variety of other enzymes, the cold-labile enzymes. A coherent change of the cell causes coordinated changes in its parts. These processes of enzymic regulation are fast, and can occur throughout a cell, practically simultaneously. Strict reductionists don't like to talk about them. "Network analysis" becomes irrelevant.

While a cell in general is activated by a wave of phosphorylation, certain processes (including glycogen synthesis) are blocked. When $BRCA_1$ or retinoblastoma protein is hyperphosphorylated, its anti-estrogenic, anti-proliferative functions are stopped. The communication between cells is another function that's stopped by injury-induced phosphorylation.

Estrogen generally activates phosphorylases, and inactivates phosphatases. Progesterone generally opposes those effects.

Phosphorylation is just one of the regulatory systems that are relevant to the development of cancer, and that are acted on oppositely by estrogen and progesterone. To reduce the explanation for cancer to a gene or two or three may be an attractive idea for molecular endocrinologists, but the idea's simplicity is delusive.

Each component of the cell contributes complexly to the cell's regulatory stability. Likewise, a drug such as RU486 complexly modifies

the cell's stability, changing thresholds in many ways, some of which synergize with progesterone (e.g., supporting the GABA system), others of which antagonize progesterone's effects (e.g., increasing exposure to prostaglandins).

There are other proteins in cells, besides the "hormone receptors," that bind progesterone, and that regulate cell functions globally. The sigma receptor, for example, that interacts with cocaine to excite the cell, interacts with progesterone to quiet the cell. The sigma receptor is closely related functionally to the histones, that regulate the activity of chromosomes and DNA, and progesterone regulates many processes that control the histones.

The GABA receptor system, and the systems that respond to glutamic acid (e.g., the "NMDA receptors") are involved in the inhibitory and excitatory processes that restrain or accelerate the growth of cancer cells, and progesterone acts through those systems to quiet cells, and restrain growth.

The inhibitor of differentiation, Id-1, is inhibited by progesterone, activated by estrogen.[8] Proteins acting in the opposite direction, PTEN and p21, for example, are activated by progesterone, and inhibited by estrogen.

The inflammatory cytokines, acting through the NFkappaB protein to activate genes, are generally oppositely regulated by estrogen and progesterone.

Prostaglandins, platelet activating factor, nitric oxide, peroxidase, lipases, histamine, serotonin, lactate, insulin, intracellular calcium, carbon dioxide, osmolarity, pH, and the redox environment are all relevant to cancer, and are affected systemically and locally by estrogen and progesterone in generally opposing ways.

About ten years ago, Geron corporation announced that it was developing products to control aging and cancer, by regulating telomerase, the enzyme that lengthens a piece of DNA at the end of the chromosomes. Their argument was that telomeres get shorter each time a cell divides, and that after about 50 divisions, cells reach the limit identified by Leonard Hayflick, and die, and that this accounts for the aging of the organism. Cancer cells are immortal, they said, because they maintain active telomerase, so the company proposed to cure cancer, by selling molecules to inhibit the enzyme, and to cure aging, by providing new enzymes for old people. However, Hayflick's limit was mainly the effect

of bad culture methods, and the theory that the shortening of telomeres causes aging was contradicted by the finding of longer telomeres in some old people than in some young people, and different telomere lengths in different organs of the same person.

But it's true that cancer cells have active telomerase, and that most healthy cells don't. It happens that telomerase is activated by cellular injury, such as radiation, that activates phosphorylases, and that it is inactivated by phosphatases. Estrogen activates telomerase, and progesterone inhibits it.

Molecular endocrinology is very important to the pharmaceutical industry, because it lends itself so well to television commercials and corporate stock offerings. Monsanto and the Pentagon believe they can use reductionist molecular biology to predict, manipulate, and control life processes, but so far it is only their ability to damage organisms that has been demonstrated.

Besides the early animal studies that showed experimentally that progesterone can prevent or cure a wide variety of tumors, the newer evidence showing that progesterone is a major protective factor against even breast cancer, would suggest that dishonest efforts to protect estrogen sales by preventing women from using natural progesterone will be causing more women to develop cancer.

The recent report that the incidence of breast cancer in the United States fell drastically between 2002 and 2004, following the great decline in estrogen sales, shows the magnitude of the injury and death caused by the falsifications of the estrogen industry—a matter of millions of unnecessary deaths, just in the years that I have been working on the estrogen issue. The current campaign against progesterone can be expected to cause many unnecessary cancer deaths (e.g., Plu-Bureau, et al., Mauvais-Jarvis, et al.), while distracting the public from the culpability of the estrogen industry.

Regeneration and Degeneration

Types of Inflammation Change with Aging

Ray Peat's Newsletter, 2012

For about 100 years it has been popular to explain the degenerative diseases as the result of mutations in the genes, a slow accumulation of "somatic mutations," as opposed to the "germ cell mutations" that are involved in Huntington's chorea and sickle cell anemia. Some people explained all the changes of aging on the same basis, but 50 years ago, the somatic mutation theory of aging was clearly shown to be false. The gene-mutation theory of cancer is more persistent, but the work of people like Harry Rubin has made it clear that functional changes in cells that are becoming cancerous destabilize the chromosomes and cause defects to appear in the genes, rather than the reverse.

Older ways of understanding aging and degenerative disease are now returning to the foreground. The developmental interactions of the organism with its environment, and the interactions of its cells, tissues, and organs with each other, have again become the focus of biological aging research. In place of the old belief that "we are defined and limited by our genes," the new perspective is showing us that we are limited by our environment, and that our environment can be modified. As we react to unsuitable environments, our internal environments become limiting for our cells, and instead of renewing themselves, repairing damage, and preparing for new challenges, our cells find themselves in blind alleys. Looking at aging in this way suggests that putting ourselves into the right environments could prevent aging.

A bird developing inside its eggshell illustrates the way organs and the environment interact. The chicken created a very good environment for the early development of its young. When the egg is formed, it contains everything needed to produce a chicken, except for oxygen and a steady warm temperature. But before the chick's body has finished developing, using yolk fat for energy, the glucose contained in the egg has been consumed, and at that point the chick's brain stops growing. A researcher who knew that brain growth in other kinds of animals requires glucose, injected glucose (or glycine) into the developing eggs when the original glucose had been depleted. The supplemental glucose allowed the chick's brain to continue growing until it hatched. These

chicks had larger brains, containing more numerous cells. The same experimenters also found that progesterone increases brain size, while corticosterone decreases it. Although the egg is a very good environment for the development of chickens, these experiments showed that it isn't the best that can be achieved. If the hen's environment had been different, it might have been able to provide as much glucose and progesterone as the experimenters did.

Mammals were able to develop bigger brains than birds, by gestating their offspring internally, allowing a continuous supply of nutrients, such as glucose, and hormones such as progesterone. But the environment of the mother still can profoundly affect the development of the offspring, by influencing her physiology.

Another factor involved in developing a large brain is the metabolic rate, which is closely associated with the temperature. Birds have larger brains relative to their bodies than reptiles do, and birds maintain a consistently high body temperature, sometimes as high as 110 degrees F, while reptiles' temperature varies somewhat according to the temperature of their surroundings and their level of activity. Amphibians have much lower metabolic rates, and are generally unable to live at the higher temperatures required by reptiles.

The high metabolic rate of a bird, combined with its development inside an egg, means that compromises are made. The high rate of metabolism uses the stored energy rapidly, so the growth of the brain is limited. But their very high body temperature maximizes the effectiveness of that brain. Birds, such as owls, parrots, and crows, that hatch in a less developed, more dependent condition, are able to continue their brain growth, and have larger brains than other birds, such as chickens. In birds and mammals, longevity generally corresponds to brain size and metabolic rate. (For example, a pet crow, Tata, died at the age of 59 in 2006 in New York; parrots sometimes live more than 100 years.) These (altricious) birds are the opposite of precocious, they preserve embryonic or infantile traits into adulthood.

For whole organisms or for single cells, development depends on the adequacy of the environment. Temperature and the quality of nourishment are important, and by thinking about the other special features of the growth processes during gestation, we might be able to find that some of the compromises that are customarily made in our more mature lives aren't necessary.

One way of looking at aging is that it's a failure of regeneration or healing, related to changes in the nature of inflammation.

In childhood, wounds heal quickly, and inflammation is quickly resolved; in extreme old age, or during extreme stress or starvation, wound healing is much slower, and the nature of the inflammation and wound closure is different. In the fetus, healing can be regenerative and scarless, for example allowing a cleft palate to be surgically corrected without scars.[1]

Fifty years ago, inflammation was seen as a necessary part of the healing process, but now it is recognized as a cause of heart disease, diabetes, cancer, and aging itself. During the development of the organism, the nature of healing changes, as the nature of inflammation changes. Early in life, healing is regenerative or restorative, and there is little inflammation. In adulthood as the amount of inflammation increases, healing fails to completely restore lost structures and functions, resulting in scarring, the replacement of functional tissue with fibrous tissue. Identifiable changes in the nature of inflammation under different conditions can explain some of these losses of healing capacity. Factors that limit inflammation and fibrosis, while permitting tissue remodeling, could facilitate regeneration and retard aging.

Several cytokines (proteins that regulate cell functions) appear at much higher concentrations in adult tissues than in fetal tissues (PDGF A, three forms of TGF, IGF-1, and bFGF[2]), and when one of these (TGF-beta1) is added to the healing fetus, it produces inflammation and fibrosis.[3] Two prostaglandins, PGE_2 and PGF2a, potently produce inflammation in fetal rabbits, but not in adult rabbits.[4]

Tissue injury that would produce inflammation in adults causes other signals in the fetus that activate repair processes. When a cell is injured or stressed, for example when deprived of oxygen, it becomes incontinent, and releases ATP into its surroundings. The extracellular ATP, and its breakdown products, ADP, AMP, adenosine, and inorganic phosphate or pyrophosphate, stimulate cells in various ways. ATP causes vasodilation, increasing circulation, and usually signals cells to divide, and can activate stem cells[5] The lactic acid produced by distressed cells also has signalling effects, including vasodilation and stimulated division. Stressed cells digest their own proteins and other structural materials (autophagy), and the breakdown products act as signals to guide the differentiation of their replacement cells. Mobile phagocytes, ingest-

ing the material of decomposing cells, are essential for guiding tissue restoration.

In adults, prostaglandins are known to be involved in many of the harmful effects of inflammation. They are formed from the polyunsaturated fats, linoleic acid and arachidonic acid, which we are unable to synthesize ourselves, so the adult's exposure to the prostaglandins is influence by diet. Since the fetus is able to synthesize fat from glucose, the newborn animal usually contains a high proportion of saturated fats and their derivatives, such as stearic acid, oleic acid, and Mead acid, which can be synthesized from glucose or amino acids. Newborn calves have very little polyunsaturated fat in their tissues, but even the small percentage of PUFA in milk causes its tissues to gradually accumulate a higher percentage of PUFA as it matures. The fatty acids of newborn humans, and other non-ruminants, reflect their mothers' diets more closely, but Mead acid is still present in human newborns.[6] In a study of prenatal learning (habituation rate), the experimenters found that the relative absence of the supposedly essential fatty acids improved the short term and long term memory of the fetus.[7] The size of the baby was found to be negatively associated with the highly unsaturated fatty acids DHA and AA,[8] showing a general growth-retarding effect of these environmentally derived fats.

The embryo or fetus is enclosed in a germ-free environment, so it doesn't need an "immune system" in the ordinary sense, but it does contain phagocytes, which are an essential part of development, in the embryo, as well as in the adult.[9] They are involved in removing malignant cells, healing wounds, and remodeling tissues. In adults, the long-chain omega-3 fatty acids such as DHA are known to be immunosuppressive, but in tests on monocytes from the umbilical cord blood of newborns, the highly unsaturated fatty acids kill the monocytes that are so important for proper development and regeneration,[10] and interfere with signals that govern their migration.[11] DHA is now being sold with many health claims, including the idea that adding it to baby formula will improve their eyesight and intelligence. As the consumption of PUFA has increased in the U.S. and many other countries, the incidence of birth defects has increased. The formation of excessive amounts of prostaglandin, or killing macrophages, among other toxic effects, might be responsible for those visible anatomical changes during growth, as well as for the subtler loss of regenerative capacity.

In the adult, the PUFA and prostaglandins are known to increase collagen synthesis. Serotonin and estrogen, which interact closely with PUFA, promote collagen synthesis and fibrosis. In the fetus, hyaluronic acid, rather than collagen, is the main extracellular material in wound repair.[12] Both it and its decomposition products have important regulatory "signal" functions in wound healing,[13] inflammation, and cell differentiation.[14]

Prostaglandins also inhibit local cell division (observed in the cornea[15]), shifting responsibility for tissue repair to mobile cells, for example stem cells from the blood. PUFA also interfere with the turnover of collagen by inhibiting proteolytic enzymes that are necessary for tissue remodeling. These are among the changes that characterize scar formation, rather than the scarless regeneration that can occur in the fetus. They also occur throughout the body with aging, as part of a progressive fibrosis.

Besides minimizing dietary PUFA, other things are known that will reduce the fibrosis associated with injury, inflammation, or aging. Thyroid hormone, progesterone, and carbon dioxide all reduce inflammation while facilitating normal tissue remodeling. Fibrosis of the heart and liver, which are often considered to be unavoidably progressive, can be regressed by thyroid hormone, and various fibroses, including breast, liver, and mesentery, have been regressed by progesterone treatment.

The thyroid hormone is necessary for liver regeneration, and the ability of the thyroid gland itself to regenerate might be related to the also great ability of the adrenal cortex to regenerate—the cells of these endocrine glands are frequently stimulated, even by intrinsic factors such as T_3 in the thyroid, and seem to have an intrinsic stem-cell-like quality, turning-over frequently. Secretion of stimulating substances is probably one of the functions of macrophages in these glands[16] The failure to recognize the glands' regenerative ability leads to many inappropriate medical treatments.

The amount of disorganized fibrous material formed in injured tissue is variable, and it depends on the state of the individual, and on the particular situation of the tissue. For example, the membranes lining the mouth, and the bones and bone marrow, and the thymus gland are able to regenerate without scarring. What they have in common with each other is a relatively high ratio of carbon dioxide to oxygen. Salamanders, which are able to regenerate legs, jaw, spinal cord, retina

and parts of the brain,[17] spend most of their time under cover in burrows, which besides preventing drying of their moist skin, keeps the ratio of carbon dioxide to oxygen fairly high.

The regeneration of fingertips, including a well-formed nail if some of the base remained, will occur if the wounded end of the finger is kept enclosed, for example by putting a metal or plastic tube over the finger. The humidity keeps the wound from forming a dry scab, and the cells near the surface will consume oxygen and produce carbon dioxide, keeping the ratio of carbon dioxide to oxygen much higher than in normal uninjured tissue.

Carbon dioxide is being used increasingly to prevent inflammation and edema. For example, it can be used to prevent adhesions during abdominal surgery, and to protect the lungs during mechanical ventilation. It inhibits the formation of inflammatory cytokines and prostaglandins,[18–20] and reduces the leakiness of the intestine.[21] Some experiments show that as it decreases the production of some inflammatory materials by macrophages (TNF[22]), including lactate, it causes macrophages to activate phagocytic neutrophils, and to increase their number and activity.[23,24]

Factors that are associated with a decreased level of carbon dioxide, such as excess estrogen and lactate, promote fibrosis. Adaptation to living at high altitude, which is protective against degenerative disease, involves reduced lactate formation, and increased carbon dioxide. It has been suggested that keloid formation (over-growth of scar tissue) is less frequent at high altitudes,[25] though this hasn't been carefully studied. Putting an injured arm or leg into a bag of pure carbon dioxide reduces pain and accelerates healing.

In aging, the removal of inactive cells becomes incomplete.[26] It is this removal of cellular debris that is essential for regenerative healing to take place. Degenerating tissue stimulates the formation of new tissue, but this requires adequate cellular energy for phagocytosis, which requires proper thyroid function. "Hyperthyroidism" has been shown to accelerate the process.[27] The active thyroid hormone, T_3, stimulates the removal of inactive cells.[28]

Regenerative healing also requires freedom from substances that inhibit the digestion of the debris. The great decline in proteolytic autophagy that occurs with aging[29] can be reduced by inhibiting the release of fatty acids. This effect is additive to the antiaging effects of

calorie restriction, suggesting that it is largely the decrease of dietary fats that makes calorie restriction effective.[30,31]

Niacinamide is a nutrient that inhibits the release of fatty acids, and it also activates phagocytic activity and lowers phosphate. It protects against the development of scars in spinal cord injuries, facilitates recovery from traumatic brain injury, and accelerates healing generally. While it generally supports immunity, it's protective against autoimmunity. It can cause tumor cells to either mature or disintegrate, but it prolongs the replicative life of cultured cells, and protects against excitotoxicity.

The amounts needed seem large if niacinamide is thought of as "vitamin B_3," but it should be considered as a factor that compensates for our unphysiological exposure to inappropriate fats. Aspirin and vitamin E are other natural substances that are therapeutic in "unnaturally" large amounts because of our continual exposure to the highly unsaturated plant-derived n-3 and n-6 fats.

When animals are made "deficient" in the polyunsaturated fatty acids, their wounds heal, with normal or accelerated collagen synthesis, and with more vigorous collagen breakdown.[32] Their blood vessels are more resistant, preventing shock that would otherwise be caused by many factors. All phases of development, from gestation to aging, are altered by the presence of the unsaturated fats, and these effects correspond closely to the loss of the regenerative capacity, the ability to replenish and restore tissues.

If the very small amounts of polyunsaturated fats reaching the fetus can retard growth and brain development[33,34] and function, it is apparently acting on some very important biological processes. The toxic effects of PUFA seen in the animal studies probably have their equivalent in humans, for example the association of childhood hyperactivity with a smaller brain. The incidence of the attention deficit-hyperactivity disorder is increasing in the U.S., somewhat faster among girls than boys.[35] In schizophrenic teenagers, the brain shrinks, suggesting an interaction of the hormones of puberty with environmental toxins or deficiencies. The progressive accumulation of much larger amounts of these fats later in life, especially after the rate of growth decreases, could be expected to cause even greater interference with those processes of development and function.

All tissues age, but the brain might be the least ambiguous organ to consider. The aging brain often shrinks, and becomes more susceptible

to excitotoxicity, which kills brain cells. Degenerative brain diseases, such as Huntington's chorea and Creutzfeld-Jacob disease, have been compared to the dementia of pellagra, in which chorea and other excitatory processes are obvious. (Anti-glutamatergic drugs are beginning to be used therapeutically, to restore some inhibitory balance in the degenerating brain.)

Pellagra occurs about twice as often in women as in men, and this is because estrogen activates an enzyme that alters metabolism of tryptophan, blocking the formation of niacin. The alternative products include the excitotoxin, quinolinic acid, and some carcinogens.

Progesterone inhibits the activity of that enzyme. Progesterone also lowers brain serotonin,[36] decreases the excitatory carcinogens[37] and increases the formation of niacin[38] The polyunsaturated fats, DHA, EPA, and linoleic acid activate the conversion of tryptophan to quinolinic acid,[39,40] and inhibit the formation of niacin.[41]

The normal pathway from tryptophan to niacin leads to formation of the coenzyme NAD, which is involved in a great variety of cellular processes, notably energy production, the maintenance of the cellular differentiated state by regulating gene expression, and the activity of phagocytes.

Glucose and niacinamide work very closely with each other, and with the thyroid hormone, in the maintenance and repair of cells and tissues. When one of these energy-producing factors is lacking, the changes in cell functions—a sort of pre-inflammatory state—activate corrective processes. Energy depletion itself is an excitatory state, that calls for increased fuel and oxygen. But when cells are exposed to PUFA, their ability to use glucose is blocked, increasing their exposure to the fats. Saturated fats activate the pyruvate dehydrogenase enzyme that is essential for the efficient use of glucose, while PUFA block it. (The MRL mouse strain has a high regenerative ability, associated with a retained tendency to metabolize glucose rather than fatty acids.) The negative energetic effects of PUFA include interfering with thyroid and progesterone. The energy resources are suppressed, at the same time that the inflammatory signals are amplified, and many regulatory pathways (including the replenishment of NAD from tryptophan) are diverted.

In the fetus, especially before the fats from the mother's diet begin to accumulate, signals from injured tissue produce the changes that lead quickly to repair of the damage, but during subsequent life, similar

signals produce incomplete repairs, and as they are ineffective they tend to be intensified and repeated, and eventually the faulty repair processes become the main problem. Although this is an ecological problem, it is possible to decrease the damage by avoiding the polyunsaturated fats and the many toxins that synergize with them, while increasing glucose, niacinamide, carbon dioxide, and other factors that support high energy metabolism, including adequate exposure to long wavelength light and avoidance of harmful radiation. As long as the toxic factors are present, increased amounts of protective factors such as progesterone, thyroid, sugar, niacinamide, and carbon dioxide can be used therapeutically and preventively.

Rosacea, Inflammation, and Aging

The Inefficiency of Stress

Ray Peat's Newsletter, 2013

ROSACEA, or acne rosacea, has been defined as "vascular and follicular dilation involving the nose and contiguous portions of the cheeks..." that may involve persistent erythema with hyperplasia of sebaceous glands. — *Stedman's Medical Dictionary* 23rd edition.

Light-skinned people, especially women between the ages of 30 and 50, sometimes develop a persistent redness of their cheeks and nose. It may begin as a tendency to flush excessively, but the blood vessels can become chronically dilated. Similar processes occur in dark-skinned people less frequently.

The eyes are sometimes involved, with redness of the exposed areas (conjuctival hyperemia). New blood vessels develop in the area, and the flow of blood through the affected tissue is greatly increased. The tissues become thickened and fibrotic, with the multiplication of fibroblasts and the increased deposition of collagen.

The cornea normally receives its oxygen from the air, and its nutrients from the aqueous humor. As rosacea of the eye develops, the blood vessels surrounding the cornea become increasingly visible, and, especially on the inner (nasal) side of the eye, the vessels tend to enlarge and become tortuous. Rhinophyma, or potato nose, has been described as a late development of rosacea.

Too often, the medical reaction is to give the condition a name, and to distinguish its variants as if they were different problems, and then to use the most direct means to eliminate the problem they have defined.

A typical attitude is that "Rosacea is an enigmatic disease with multiple exacerbations and remissions, and, unfortunately, treatment is directed toward symptomatic control rather than cure" (Randleman).

Lasers or other radiation, caustic chemical abrasion, surgical planing and dermal shaves, and other forms of surgery may be used to destroy the superficial blood vessels, and to reduce the enlarged nose or other irregularities. A few decades ago, when rosacea was believed to be the result of a local infection, antibiotics were used to treat it, and some of them, including tetracycline, helped. It was discovered that some antibiotics have anti-inflammatory actions, apart from their germicidal effects,

and now it is very common to prescribe the chronic use of tetracycline to suppress symptoms.

Rosacea, and the fibrotic changes associated with it (pingueculae and pterygia in the eyes, rhinophyma of the nose, etc.), are much more than "cosmetic" issues, involving the skin and eye surface. If the invasive proliferation of blood vessels can be prevented, it's important to do that, because, for example, pannus/neovascularization of the cornea can seriously impair vision.

But possibly the strangest thing about the relationship of the medical profession to rosacea is that its essential features, invasive neovascularization and fibrotic growth, are of great interest when they occur elsewhere, and many physiological processes are known to regulate the growth of blood vessels and fibroblasts, but nearly all the attention given to rosacea and rhinophyma concerns control of symptoms for cosmetic effect. Rosacea is a physiological problem that deserves consideration in the light of all that's known about physiology and developmental biology.

The increased incidence of rosacea after the age of 30, and the fact that it occurs most commonly in the areas that are most exposed to sunlight (bald men sometimes develop it on the top of the head), indicate that aging and irritation are essential causes. Stress, irritation (such as produced by ultraviolet or ionizing radiation or free radicals), and aging are known to cause disorganized growth of fibrous and vascular tissues in various parts of the body. The occurrence of these processes at the surface, where the changes can be observed immediately, and without invasive procedures, should have aroused wide interest among those who study kidney disease, diabetes, and other degenerative diseases in which fibrosis and neovascularization play important roles.

A localized stress or irritation at first produces vasodilation that increases the delivery of blood to the tissues, allowing them to compensate for the stress by producing more energy. Some of the agents that produce vasodilation also reduce oxygen consumption (nitric oxide, for example), helping to restore a normal oxygen tension to the tissue. Hypoxia itself (produced by factors other than irritation) can induce vasodilation, and if prolonged sufficiently, tends to produce neovascularization and fibrosis.

Sensitivity to the harmful effects of light can be increased by some drugs and by excess porphyrins produced in the body (and by the porphyrin precursor, delta-amino levulinic acid), leading to rosacea, so those

factors should be considered, but too often alcohol (which can cause porphyrin to increase) is blamed for rosacea and rhinophyma, without justification. There are many ways in which poor health can increase light sensitivity. Some types of excitation produced by metabolites (or by the failure of inhibitory metabolites) can produce vasodilation, involving the release of nitric oxide,[1] setting off a series of potentially pathological reactions, including fibrosis. The nitric oxide increases glycolysis while lowering energy production. The excitatory metabolite glutamate, and nitric oxide, are both inhibited by aspirin.[2]

When blood flow in skin affected by rosacea was measured, circulation was 3 or 4 times higher than normal,[3] and oxygen tension may be increased. An inability to extract oxygen from the blood, or to use it to produce energy, will produce the same hyperemia that would be produced by a lack of oxygen. These measurements suggest that mitochondrial defects would be the best place to look for a general cause of rosacea.

When mitochondria are damaged, active cells produce increased amounts of lactic acid, even in the presence of adequate oxygen. Otto Warburg identified this kind of metabolism, aerobic glycolysis, as an essential feature of cancer, and showed that it could be produced by stress, ionizing radiation, carcinogenic toxins, and even by a simple oxygen deficiency. Other investigators around the same time showed that lactic acid produces vasodilation (for example, in the cornea), and more recently it has been shown to promote the development of fibrosis, and it has been called a "phlogogen," a promoter of inflammation.

Riboflavin, vitamin B_2, is an essential component of the mitochondrial respiratory enzymes, and it is very easily destroyed by light (blue light and especially ultraviolet). When it is excited by high energy light, it can spread the damage to other components of the mitochondria, including the cytochromes and the polyunsaturated fatty acids. The other B vitamins are affected when riboflavin's actions are disturbed.

Vitamin K is also extremely light sensitive, and it interacts closely with coenzyme Q in regulating mitochondrial metabolism. For example, mitochondrial Complex-I, NADH-ubiquinone reductase, is probably the most easily damaged part of the mitochondrion, and it is protected by vitamin K. Vitamin E, coenzyme Q, and the polyunsaturated fatty acids are also light sensitive, and they are more susceptible to free radical damage when vitamin K is deficient.

Niacinamide, one of the B vitamins, provides energy to this mitochondrial system. Under stress and strong excitation, cells waste niacinamide-NADH, but niacinamide itself has a sedative antiexcitatory effect, and some of its actions resemble a hormone. Estrogen tends to interfere with the formation of niacin from tryptophan. Tryptophan, rather than forming the sedative niacin (pyridine carboxylic acid), can be directed toward formation of the excitatory quinolinic acid (pyridine dicarboxylic acid) by polyunsaturated fatty acids. Excitation must be in balance with a cell's energetic resources, and niacinamide can play multiple protective roles, decreasing excitation, increasing energy production, and stabilizing repair systems. The state of excitation and type of energy metabolism are crucial factors in governing cell functions and survival.

The polyunsaturated fatty acids, besides their interactions with estrogen and tryptophan metabolism, promote excitation and decrease energy production in several other ways. For example, they increase the excitatory effects of the glutamate pathways,[4,5] and their breakdown products inhibit mitochondrial respiration.[6–8]

The excess excitation that produces nitric oxide and lactic acid lowers the energy production of vascular cells, possibly enough to lower their contractile ability,[9] causing vasodilation. When flushing is caused by a mismatch between energy supply and energy demand, caffeine can decrease the vasodilation,[10] but when vasodilation is caused more physiologically by carbon dioxide, caffeine doesn't have that effect.[11] In a study in which drinking hot water or coffee was compared with drinking room-temperature coffee or caffeine, it was found that the hot liquids caused flushing, but cool coffee and caffeine didn't.

Caffeine increases cells' energy efficiency, and by opposing the effects of adenosine (secreted by cells that are stressed and energy-depleted), it can inhibit vasodilation, angioneogenesis,[12,13] and fibrosis.[14]

One nearly ubiquitous source of inappropriate excitation and energy depletion is the endotoxin, bacterial lipopolysaccharides absorbed from the intestine.[15] That this ubiquitous toxin has a role in rosacea is suggested by the observation that intestinal stimulation, to speed transit through the bowel, immediately relieved symptoms.[16] Increased cortisol[17] and sepsis[18] interfere with mitochondrial energy production.

Simple nervous blushing or flushing is usually considered harmless, and when a person is overheated, the reddening of the skin has the function of facilitating heat loss, to restore a normal temperature. But

even nerve-regulated flushing can involve a distinct interference with mitochondrial respiration, and can stimulate the overgrowth of blood vessels.

Cancer's respiratory defect that Warburg identified, fermentation with lactic acid production even in the presence of adequate oxygen, was the result of some kind of injury to the mitochondria. He showed that one of the injuries that could produce aerobic glycolysis was a deficiency of riboflavin. He observed that tumors generally were anoxic, and that cancers typically appeared in the midst of tissue that was atrophying, and suggested that the cancer cells' survival was favored by their ability to live without oxygen. This may be relevant to the observations of many surgeons of a small cancer embedded in the fibrous tissue of large rhinophymas that have been removed.

The relatively high incidence of rosacea among women (some studies indicate that it may be 3 times as common in women as in men) isn't likely to be the result of greater sun exposure, so it's reasonable to look for hormonal causes.

In old age, it's well recognized that men's estrogen level rises. But the estrogen industry has convinced women that their estrogen declines as they get older. It's common knowledge that aging rodents often go into "persistent estrus," and that their estrogen levels generally increase with age.[19,20] Several studies in women have shown that serum estrogen levels rise from the teens into the 40s.[21–23]

Other studies show that serum and tissue estrogen concentrations are not concordant, and that some tissues may contain several times as much estrogen as the serum.[24] Local irritation increases tissue estrogen content.

The antiestrogens, especially progesterone, begin declining in the 30s, so that the rising estrogen has more effect on the tissues during those years. These are the years in which the incidence of rosacea rises suddenly. Rosacea develops later on average in men, whose estrogen levels rise significantly at later ages.

Estrogen's most immediate effect on cells is to alter their oxidative metabolism. It promotes the formation of lactic acid. In the long run, it increases the nutritional requirements for the B vitamins, as well as for other vitamins. It also increases the formation of aminolevulinic acid, a precursor of porphyrin, and increases the risk of excess porphyrin increasing light sensitivity. Both aminolevulinic acid and excess por-

phyrins are toxic to mitochondria, apart from their photosensitizing actions. Nitric oxide, glutamate, and cortisol all tend to be increased by estrogen.

Veins and capillaries are highly sensitive to estrogen, and women are more likely than men to have varicose veins, spider veins, leaky capillaries, and other vascular problems besides rosacea. Estrogen can promote angioneogenesis by a variety of mechanisms, including nitric oxide.[25] "Estrogens potentiate corticosteroid effects on the skin such as striae, telangiectasiae, and rosacea dermatitis".[26] Early forms of oral contraceptives, high in estrogen, were found to increase acne rosacea more than three-fold.[27]

Lactic acid, produced under the influence of estrogen, nitric oxide, or other problems of energy formation, besides causing vasodilation, also stimulates the growth of fibroblasts. Oxygen deprivation, or damage to mitochondria, will increase lactic acid formation, and so it will immediately cause vasodilation, and if the problem is prolonged, new blood vessels will grow, and fibrous connective tissue will increase. Estrogen stimulates collagen synthesis, and it has been associated with a variety of inflammatory and fibrotic conditions.[28,29]

The cornea normally contains more riboflavin even than the retina, which has a much higher rate of metabolism. When the cornea isn't able to get enough oxygen from the air for its needs (and if riboflavin is deficient, its need for oxygen is increased), surrounding blood vessels at first dilate in response to the diffusing lactic acid, to increase the blood supply to the edges of the cornea. If the problem is prolonged, the conjuctiva becomes chronically blood-shot, hyperemic, and larger more visible blood vessels grow, surrounding the cornea, or even invading the cornea. Many people, especially women, experienced problems of this sort from wearing contact lenses, especially when the lenses were made of materials very impermeable to oxygen.[30]

Sunlight, and mechanical obstruction of the cornea, produce very localized effects, but those local effects are more likely to be harmful when there is a systemic nutritional deficiency or excess of estrogen. When the systemic problem is very severe, the cheeks, nose, and eyes might not be the first tissues to experience a functional disturbance.

The mitochondrial inhibition produced by the action of the parasympathetic nervous system (occurring in simple blushing) can occur wherever those nerves act, and blood vessels in all parts of the body are

responsive to the acetylcholine secreted by those nerves. Sleep typically involves a shift of dominance in the autonomic nervous system toward the parasympathetic nerves, with vasodilation. Nosebleeds, especially in children, commonly occur during sleep.[31]

A 3 year-old child who had been having an average of 3 nosebleeds every day, during a nap and at night, for several months, also had an extreme behavior problem. He became angry and sometimes violent when he went a little longer than normal between meals. After an oral dose of about ten milligrams of riboflavin, he was able to sleep without having another recurrence of the nosebleeds, and his tantrums became rare. Apparently, the nerve-regulated vasodilation produced by sleep, combined with a riboflavin deficiency, had been enough to produce nosebleeds. The energy deficit resulting from a systemic riboflavin deficiency had probably been causing him to be abnormally sensitive to glycogen depletion, producing sudden anger. In another individual, the energy problem might have taken the form of a memory problem, or of a hemorrhage in the brain or other essential organ.

A 37 year old slightly alcoholic man with a bright red nose and cheeks was an amateur fiction writer, but he was having trouble with his memory for words, and for everyday events. Even conversationally, he had to struggle for relatively familiar words. On the suggestion that riboflavin might help his memory, by allowing his brain cells to use oxygen more efficiently, he had his doctor give him an intravenous injection of B vitamins. When I saw him the next day, his conversation was perfectly fluent, and he obviously had easy access to a good vocabulary. Just as noticeable was the normal color of his nose and cheeks. For a week, he had a daily injection of the B vitamins, and his nose color and vocabulary stayed normal. But on the weekend, after not having the shots for two days, his nose and cheeks were again maraschino cherry red, and his speech was halting, as he struggled for words. He forgot the whole episode, and neglected to return to the doctor for more of the vitamin injections. Ten years later, he had developed a medium-sized potato nose, and had his heart valves replaced.

His vitamin requirements were apparently abnormally high. At first, the problems resulting from damaged mitochondria seem mostly functional (flushing, mood, memory problems, etc.) and variable, but chronically disturbed functions lead to structural, anatomical changes, as prolonged stimulation alters tissue maintenance and growth.

Abram Hoffer, who had been treating schizophrenia and senile dementia with niacin, accidentally discovered that it cured his bleeding gums. That led to its use to treat heart disease.

The "orthomolecular" ideas of Hoffer and Linus Pauling were developed in a context of biochemistry governed by genetics, molecular biology, in which the goal was to provide a chemical that was lacking because of a genetic defect in metabolism. Their idea of using nutrients as drugs has led to many unphysiological practices, in which an isolated nutrient is supposed to have a drug-like action, and if in isolation it doesn't act like a drug, then it should be used only according to the normal genetically determined nutritional requirement.

But in reality, nutritional requirements are strongly influenced by history and present circumstances. For example, when corneal mitochondria have been damaged by riboflavin deficiency, they have been found to subsequently require more than the normal amount of the vitamin to function properly. And the presence of a certain amount of one nutrient often increases or decreases the amount of other nutrients needed.

When the interactions among energy expenditure and energy production, and cellular activation and cellular inhibition, are taken into account, then it's clear that any particular problem is likely to have many causes and many factors that could contribute to a cure.

Lactate, glutamate, ammonium, nitric oxide, quinolinate, estrogen, histamine, aminolevulinate, porphyrin, ultraviolet light, polyunsaturated fatty acids and endotoxin contribute to excitatory and excitotoxic processes, vasodilation, angioneogenesis, and fibrosis.

Carbon dioxide, glycine, GABA, saturated fatty acids,[32] vitamin K, coenzyme Q_{10}, niacinamide, magnesium, red light, thyroid hormone, progesterone, testosterone, and pregnenolone are factors that can be increased to protect against inappropriate cellular excitation.

All of the nutritional factors that participate in mitochondrial respiration contribute to maintaining a balance between excessive excitation and protective inhibition. Riboflavin, coenzyme Q_{10}, vitamin K, niacinamide, thiamine, and selenium are the nutrients that most directly relate to mitochondrial energy production.

Coffee is often avoided by people with rosacea, but it is a very good source of niacin and magnesium, and caffeine has some of the same cell-protective functions as niacinamide.

People suffering from rosacea have been found to be more likely than average to have suffered from styes in childhood, to have varicose veins and spider veins, and to suffer from migraines and depression.

Hypothyroidism has been identified as a factor in all of those. Good thyroid function is necessary for resistance to bacterial infection, for regulation of blood sugar, neurotransmitters, and hormones related to mood, and for the formation of progesterone. Progesterone regulates smooth muscle tone, including the walls of veins, so that a deficiency allows veins to enlarge. It also prevents overgrowth of fibrotic tissue, and in some contexts may inhibit angioneogenesis.

GABA itself tends to raise body temperature,[33] by controlling vasodilation, and the factors such as progesterone which protect mitochondrial energy production are also thermogenic, supporting the GABA system. Flushing, both by directly causing heat loss and by reducing mitochondrial energy production, tends to lower body temperature.

The sun-damaged areas in rosacea can be directly provided with some of the protective factors by applying them topically. In the same way that topical lactate can cause vasodilation and disturbed energy metabolism,[34] topical niacinamide, progesterone, vitamin K, and coenzyme Q_{10} can improve the metabolism and function of the local tissues. Riboflavin can probably be useful when applied topically, but because of its extreme sensitivity to light, it should usually be used only internally, unless the treated skin is covered to prevent exposure to light. Topically applied caffeine, even after sun exposure, can reduce local tissue damage.[35] Aspirin and saturated fats can also be protective when applied topically.

Some of the benefit from antibiotics probably results from the reduced endotoxin stress when intestinal bacteria are suppressed. However, antibiotics can kill the intestinal bacteria that produce vitamin K, so it's important to include that in the diet when antibiotics are used.

Some fibers, such as raw carrots, that are effective for lowering endotoxin absorption also contain natural antibiotics, so regular use of carrots should be balanced by occasional supplementation with vitamin K, or by occasionally eating liver or broccoli.

Abram Hoffer's research was instrumental in getting niacin recognized as a heart protective drug, but nearly everyone who prescribes it does so to lower blood lipids. That wasn't Hoffer's understanding of its function. He thought it acted directly on blood vessels to protect their

integrity. During his studies of its effects on heart disease, he saw that it also lowered cancer mortality, and so began treating cancer patients with it, with considerable success, but there was no medical cliché that could allow the profession to follow in that direction.

The arguments I have outlined for considering rosacea to be essentially a problem of metabolic energy, and the mechanisms that I mention for restoring mitochondrial functions, might seem more complex than Hoffer's orthomolecular views. However, this approach is actually much simpler conceptually than any of the ideologies of drug treatment. It simply points out that certain excitatory factors can interfere with energy production, and that there are opposing "inhibitory" factors that can restore energy efficiency. Sometimes, using just one or two of the factors can be curative.

Because mitochondrial respiration is very similar in every kind of tissue, a physiological view of rosacea could incline us toward considering the effects of these metabolic factors in other organs during stress and aging—what would the analogous condition of rosacea and rhinophyma be in the brain, heart, liver, or kidney?

Salt, Energy, Metabolic Rate, and Longevity

Ray Peat's Newsletter, 2007

In the 1950s, when the pharmaceutical industry was beginning to promote some new chemicals as diuretics to replace the traditional mercury compounds, Walter Kempner's low-salt "rice diet" began to be discussed in the medical journals and other media. The diuretics were offered for treating high blood pressure, pulmonary edema, heart failure, "idiopathic edema," orthostatic edema and obesity, and other forms of water retention, including pregnancy, and since they functioned by causing sodium to be excreted in the urine, their sale was accompanied by advising the patients to reduce their salt intake to make the diuretic more effective.

It was clear to some physicians (and to most veterinarians) that salt restriction, especially combined with salt-losing diuresis, was very harmful during pregnancy, but that combination became standard medical practice for many years, damaging millions of babies.

Despite numerous publications showing that diuretics could cause the edematous problems that they were supposed to remedy, they have been one of the most profitable types of drug. Dietary salt restriction has become a cultural cliché, largely as a consequence of the belief that sodium causes edema and hypertension.

Salt restriction, according to a review of about 100 studies,[1] lowers the blood pressure a few points. But that generally doesn't relate to better health. In one study (3000 people, 4 years), there was a clear increase in mortality in the individuals who ate less salt. An extra few grams of salt per day was associated with a 36 % reduction in "coronary events."[2] Another study (more than 11,000 people, 22 years) also showed an inverse relation between salt intake and mortality.[3]

Tom Brewer, an obstetrician who devoted his career to educating the public about the importance of prenatal nutrition, emphasizing adequate protein (especially milk), calories, and salt, was largely responsible for the gradual abandonment of the low-salt plus diuretics treatment for pregnant women. He explained that sodium, in association with serum albumin, is essential for maintaining blood volume. Without adequate sodium, the serum albumin is unable to keep water from leaving the

blood and entering the tissues. The tissues swell as the volume of blood is reduced.

During pregnancy, the reduced blood volume doesn't adequately nourish and oxygenate the growing fetus, and the reduced circulation to the kidneys causes them to release a signal substance (renin) that causes the blood to circulate faster, under greater pressure. A low salt diet is just one of the things that can reduce kidney circulation and stimulate renin production. Bacterial endotoxin, and other things that cause excessive capillary permeability, edema, or shock-like symptoms, will activate renin secretion.

The blood volume problem isn't limited to the hypertension of pregnancy toxemia: "Plasma volume is usually lower in patients with essential hypertension than in normal subjects".[4]

Several studies of preeclampsia or toxemia of pregnancy showed that supplementing the diet with salt would lower the women's blood pressure, and prevent the other complications associated with toxemia.[5]

It has been known for many years that decreasing sodium intake causes the body to respond adaptively, increasing the renin-angiotensin-aldosterone system (RAAS). The activation of this system is recognized as a factor in hypertension, kidney disease, heart failure, fibrosis of the heart, and other problems. Sodium restriction also increases serotonin, activity of the sympathetic nervous system, and plasminogen activator inhibitor type-1 (PAI-1), which contributes to the accumulation of clots and is associated with breast and prostate cancer. The sympathetic nervous system becomes hyperactive in preeclampsia.[6]

Despite the general knowledge of the relation of dietary salt to the RAA system, and its application by Brewer and others to the prevention of pregnancy toxemia, it isn't common to see the information applied to other problems, such as aging and the stress-related degenerative diseases.

Many young women periodically crave salt and sugar, especially around ovulation and premenstrually, when estrogen is high. Physiologically, this is similar to the food cravings of pregnancy. Premenstrual water retention is a common problem, and physicians commonly offer the same advice to cycling women that was offered as a standard treatment for pregnant women—the avoidance of salt, sometimes with a diuretic. But when women premenstrually increase their salt intake according to their craving, the water retention can be prevented.

Blood volume changes during the normal menstrual cycle, and when the blood volume is low, it is usually because the water has moved into the tissues, causing edema. When estrogen is high, the osmolarity of the blood is low.[7,8] Hypothyroidism (which increases the ratio of estrogen to progesterone) is a major cause of excessive sodium loss.

The increase of adrenalin caused by salt restriction has many harmful effects, including insomnia. Many old people have noticed that a low sodium diet disturbs their sleep, and that eating their usual amount of salt restores their ability to sleep. The activity of the sympathetic nervous system increases with aging, so salt restriction is exacerbating one of the basic problems of aging. Chronically increased activity of the sympathetic (adrenergic) nervous system contributes to capillary leakage, insulin resistance (with increased free fatty acids in the blood), and degenerative changes in the brain.[9]

The flexibility of blood vessels (compliance) is decreased by a low-salt diet, and vascular stiffness caused by over-activity of the sympathetic nervous system is considered to be an important factor in hypertension, especially with aging.

Pregnancy toxemia/preeclampsia involves increased blood pressure and capillary permeability, and an excess of prolactin. Prolactin secretion is increased by serotonin, which is one of the substances increased by salt restriction, but prolactin itself can promote the loss of sodium in the urine,[10] and contributes to vascular leakage and hypertension.

In pregnancy, estrogen excess or progesterone deficiency is an important factor in the harmful effects of sodium restriction and protein deficiency. A deficiency of protein contributes to hypothyroidism, which is responsible for the relative estrogen excess.

Protein, salt, thyroid, and progesterone happen to be thermogenic, increasing heat production and stabilizing body temperature at a higher level. Prolactin and estrogen lower the temperature set-point.

The downward shift of temperature and energy metabolism in toxemia or salt deprivation tends to slow the use of oxygen, increasing the glycolytic use of sugar, and contributing to the formation of lactic acid, rather than carbon dioxide. In preeclampsia, serum lactate is increased, even while free fatty acids are interfering with the use of glucose.

One way of looking at those facts is to see that a lack of sodium slows metabolism, lowers carbon dioxide production, and creates inflammation, stress and degeneration. Rephrasing it, sodium stimulates energy

metabolism, increases carbon dioxide production, and protects against inflammation and other maladaptive stress reactions.

In recent years, Weissman's "wear-and-tear" theory of aging, and Pearl's "rate of living" theory have been clearly refuted by metabolic studies that are showing that intensified mitochondrial respiration decreases cellular damage, and supports a longer life-span.

Many dog owners are aware that small dogs eat much more food in proportion to their size than big dogs do. And small dogs have a much greater life expectancy than big dogs, in some cases about twice as long.[11]

Organisms as different as yeasts and rodents show a similar association of metabolic intensity and life-span. A variety of hamster with a 20% higher metabolic rate lived 15% longer than hamsters with an average metabolic rate.[12]

Individuals within a strain of mice were found to vary considerably in their metabolic rate. The 25% of the mice with the highest rate used 30% more energy (per gram of body weight) than the 25% with the lowest metabolic rate, and lived 36% longer.[13]

The mitochondria of these animals are "uncoupled," that is, their use of oxygen isn't directly proportional to the production of ATP. This means that they are producing more carbon dioxide without necessarily producing more ATP, and that even at rest they are using a considerable amount of energy.

One important function of carbon dioxide is to regulate the movement of positively charged alkali metal ions, such as sodium and calcium. When too much calcium enters a cell it activates many enzymes, prevents muscle and nerve cells from relaxing, and ultimately kills the cell. The constant formation of acidic carbon dioxide in the cell allows the cell to remove calcium, along with the small amount of sodium which is constantly entering the cell.

When there is adequate sodium in the extracellular fluid, the continuous inward movement of sodium ions into the resting cell activates an enzyme, sodium-potassium ATPase, causing ATP to break down into ADP and phosphate, which stimulates the consumption of fuel and oxygen to maintain an adequate level of ATP. Increasing the concentration of sodium increases the energy consumption and carbon dioxide production of the cell. The sodium, by increasing carbon dioxide production, protects against the excitatory, toxic effects of the intracellular calcium.

Hypertonic solutions, containing more than the normal concentration of sodium (from about twice normal to 8 or 10 times normal) are being used to resuscitate people and animals after injury. Rather than just increasing blood volume to restore circulation, the hypertonic sodium restores cellular energy production, increasing oxygen consumption and heat production while reducing free radical production, improves the contraction and relaxation of the heart muscle, and reduces inflammation, vascular permeability, and edema.

Seawater, which is hypertonic to our tissues, has often been used for treating wounds, and much more concentrated salt solutions have been found effective for accelerating wound healing.[14]

There have been several publications suggesting that increasing the amount of salt in the diet might cause stomach cancer, because countries such as Japan with a high salt intake have a high incidence of stomach cancer.

Studies in which animals were fed popular Japanese foods—"salted cuttlefish guts, broiled, salted, dried sardines, pickled radish, and soy sauce"—besides a chemical carcinogen, showed that the Japanese foods increased the number of tumors. But another study, adding only soy sauce (with a salt content of about 18 %) to the diet did not increase the incidence of cancer, in another it was protective against stomach cancer.[15] Several studies show that dried fish and pickled vegetables are carcinogenic, probably because of the oxidized fats, and other chemical changes, and fungal contamination, which are likely to be worse without the salt. Animals fed dried fish were found to have mutagenic urine, apparently as a result of toxic materials occurring in various preserved foods.[16]

Although preserved foods develop many peculiar toxins, even fresh fish in the diet have been found to be associated with increased cancer risk.[17]

When small animals were given a milliliter of a saturated salt solution with the carcinogen, the number of tumors was increased with the salt. However, when the salt was given with mucin, it had no cancer promoting effect. Since the large amount of a saturated salt solution breaks down the stomach's protective mucus coating, the stomach cells were not protected from the carcinogen. Rather than showing that salt causes stomach cancer, the experiments showed that a cup or more

of saturated salt solution, or several ounces of pure salt, shouldn't be ingested at the same time as a strong carcinogen.

Some studies have found pork to be associated with cancer of the esophagous,[18] thyroid,[19] and other organs, but an experiment with beef, chicken, or bacon diet in rats provides another perspective on the role of salt in carcinogenesis. After being given a carcinogen, rats were fed meat diets, containing either 30 % or 60 % of freeze-dried fried beef, chicken, or bacon. Neither beef nor chicken changed the incidence of precancerous lesions in the intestine, but the incidence was reduced by 12 % in the animals on the 30 % bacon diet, and by 20 % in rats getting the diet with 60 % bacon. Salt apparently made the difference.

Other protective effects of increased sodium are that it improves immunity,[20] reduces vascular leakiness, and alleviates inflammation.[21] All of these effects would tend to protect against the degenerative diseases, including tumors, atherosclerosis, and Alzheimer's disease. The RAA system appears to be crucially involved in all kinds of sickness and degeneration, but the protective effects of sodium are more basic than just helping to prevent activation of that system.

A slight decrease in temperature can promote inflammation.[22] The thermogenic substances—dietary protein, sodium, sucrose, thyroid and progesterone—are antiinflammatory for many reasons, but very likely the increased temperature itself is important.

A poor reaction to stress, with increased cortisol, can raise the body temperature by accelerating the breakdown and resynthesis of proteins, but adaptive resistance to stress increases the temperature by increasing the consumption of oxygen and fuel. In the presence of increased cortisol, abdominal fat increases, along with circulating fatty acids and calcium, as mitochondrial respiration is suppressed.

When mice are chilled, they spontaneously prefer slightly salty water, rather than fresh, and it increases their heat production.[23] When rats are given 0.9 per cent sodium chloride solution with their regular food, their heat production increases, and their body fat, including abdominal fat, decreases.[24] These responses to increased dietary sodium are immediate. Part of the effect of sodium involves regulatory processes in the brain, which are sensitive to the ratio between sodium and calcium. Decreasing sodium, or increasing calcium, causes the body's metabolism to shift away from thermogenesis and accelerated respiration.

Regulating intracellular calcium by increasing the production of carbon dioxide is probably a basic mechanism in sodium's protection against inflammation and excitatory cell damage and degeneration.

Cortisol's suppression of mitochondrial respiration is closely associated with its ability to increase intracellular calcium. Cortisol blocks the thermogenic effects of sodium, allowing intracellular calcium to damage cells. With aging, the tissues are more susceptible to these processes.

The thermogenic effects of sodium can be seen in long-term studies, as well as short. A low-sodium diet accelerates the decrease in heat production that normally occurs with aging, lowering the metabolic rate of brown fat and body temperature, and increasing the fat content of the body, as well as the activity of the fat synthesizing enzyme.[25]

Activation of heat production and increased body temperature might account for some of the GABA-like sedative effects of increased sodium. Increasing GABA in the brain increases brown fat heat production.[26] Activation of heat production by brown fat increases slow wave sleep,[27] the loss of which is characteristic of aging. (In adult humans, the skeletal muscles have heat-producing functions similar to brown fat.)

Now that inflammation is recognized as having a central role in the degenerative diseases, the fact that renin, angiotensin, and aldosterone all contribute to inflammation and are increased by a sodium deficiency, should arouse interest in exploring the therapeutic uses of sodium supplementation, and the integrated use of all of the factors that normally support respiratory energy production, especially thyroid and progesterone. Progesterone's antagonism to aldosterone has been known for many years, and the synthetic antialdosterone drugs are simply poor imitations of progesterone.

But the drug industry is interested in selling new drugs to block the formation and action of each of the components of the RAAS, rather than an inexpensive method (such as nutrition) to normalize the system.

Serotonin, Depression, and Aggression

The Problem of Brain Energy

Ray Peat's Newsletter, 2012

ANYONE who has been reading the mass media and watching television in recent decades is familiar with the use of tryptophan as an antidepressant. Tryptophan is easily converted to serotonin and melatonin in the body. The most popular kind of antidepressant, the "serotonin reuptake inhibitor," is said to act by increasing the action of serotonin in the brain. Many people have read articles in popular science magazines explaining that a deficiency of serotonin can cause depression, suicide, and aggression. Estrogen is often said to achieve its "wonderful" effects by increasing the effects of serotonin.

Reserpine is an ancient tranquilizer, derived from a plant used in India for centuries. It has a powerful tranquilizing action, has been used to treat hypertension, and was found to be an antidepressant (Davies and Shepherd, 1955). It lowers the concentration of serotonin in the brain and other tissues. Isoniazid, an antidepressant that came into use in the 1950s, is effective, but it probably has no effect on serotonin. When those drugs were popular, serotonin wasn't recognized as a "neurotransmitter." It wasn't until the 1960s that our present set of doctrines regarding serotonin's effects on mood and behavior came into being.

> Extremely serious mistakes about the nature of the solar system didn't matter too much until interplanetary travel became a possibility. Extremely serious mistakes about brain "transmitters" and "receptors" didn't matter too much until the drug industry got involved.
>
> "Three years before Prozac received approval by the US Food and Drug Administration in late 1987, the German BGA, that country's FDA equivalent, had such serious reservations about Prozac's safety that it refused to approve the antidepressant based on Lilly's studies showing that previously nonsuicidal patients who took the drug had a fivefold higher rate of suicides and suicide attempts than those on older antidepressants, and a threefold higher rate than those taking placebos."
>
> "Using figures on Prozac both from Lilly and independent research, however, Dr. David Healy, an expert on the brain's serotonin system and director of the North Wales Department of Psychological Medicine at the University of Wales, estimated that probably 50,000 people have committed suicide on Prozac since its launch, over and above the number who would have done so if left untreated."
>
> — The Boston Globe, 2000.

Serotonin research is relatively new, but it rivals estrogen research for the level of incompetence and apparent fraudulent intent that can be found in professional publications.

This is partly because of the involvement of the drug industry, but the U.S. government also played a role in setting a pattern of confused and perverse interpretation of serotonin physiology, by its policy of denigrating and incriminating LSD, a powerful serotonin (approximate) antagonist, by any means possible, for example claiming that it causes genetic damage and provokes homicidal or suicidal violence. The issue of genetic damage was already disproved in the 1960s, but this was never publicly acknowledged by the National Institutes of Mental Health or other government agency. The government's irresponsible actions helped to create the drug culture, in which health warnings about drugs were widely disregarded, because the government had been caught in blatant fraud. In more recent years, government warnings about tryptophan supplements have been widely dismissed, because the government has so often lied. Even when the public health agencies try to do something right, they fail, because they have done so much wrong.

In animal studies LSD, and other anti-serotonin agents, increase playfulness and accelerate learning, and cause behavioral impairment only at very high doses. While reserpine was used medically for several decades, and was eventually found to have harmful side effects, medical research in LSD was stopped before its actual side effects could be discovered. The misrepresentations about LSD, as a powerful antiserotonin agent, allowed a set of cultural stereotypes about serotonin to be established. Misconceptions about serotonin and melatonin and tryptophan, which are metabolically interrelated, have persisted, and it seems that the drug industry has exploited these mistakes to promote the "new generation" of psychoactive drugs as activators of serotonin responses. If LSD makes people go berserk, as the government claimed, then a product to amplify the effects of serotonin should make people sane.

The "serotonin reuptake inhibitors" are called the "third generation" of antidepressants. The monoamine oxidase (MAO) inhibitors, that came into use in the 1950s, are called the "first generation." When their patents expire on a "generation" of drugs, the drug companies find reasons for claiming that the new drugs are better. Every doctor in the country seems to know that the old MAO-inhibitors are dangerous because they can raise blood pressure if you eat certain kinds of cheese

while taking them. In fact, statistics show that they are safer than the new generation of antidepressants. It is hardly possible for a physician to prescribe the most appropriate drug, because the medical licensing boards are thoroughly indoctrinated by the drug companies, to believe that the safest and most effective drugs are those whose patents are still in force.

While it is true that the newer antidepressants increase the actions of serotonin, it is not true that this explains their antidepressant action. This is a culturally conditioned promotional construction. Since different antidepressants increase, decrease, or don't affect the actions of serotonin, a radically new kind of theory of depression and the antidepressants is needed. Theories based on "transmitter" substances and "receptors" are favored by the drug industry, but that kind of thinking is hardly better than the belief in demons and their exorcism. If an herbal tea cures depression because the demon doesn't like its smell, at least the patient never has to abandon a remedy because a tea patent has expired.

In the world of "neurotransmitters" and "receptors," there is ample room for the development of speculative mechanisms of drug action. Serotonin is regulated by the rate of its synthesis and degradation, by its uptake, storage, and release, and by its transporters, and its effects are modified by a great variety of receptors, by the number of these receptors, and by their binding affinities and competitive binders. "Different receptors" are defined by the effects of chemicals other than serotonin; this means that serotonin itself hypothetically gains some of the properties of every substance that shows some binding competition with serotonin. This complexity[†] has made it possible to argue that a given condition is caused by either an excess or a deficiency of serotonin.

The drug companies like to call some of their new products SSRI, "selective serotonin reuptake inhibitors," meaning that they don't indiscriminately increase all the biogenic amines, the way the old MAO inhibitors supposedly did. Every drug does many things, each a little differently, so it's technically true to say that they "selectively" do this or that. But the term "antidepressant," as distinguished from "tranquilizer," says that the drug is intended to relieve depression. Injecting serotonin never does that, but sometimes adrenalin or dopamine does, and these "SSRI" drugs increase the activities of those other amines enough that those changes could explain the altered mood, if it weren't for the need to speak of a "new generation of drugs." Injecting serotonin, or increas-

ing its activity, can cause sedation, helplessness, or apathy, but these drugs have that effect only some of the time. Therefore, they aren't called tranquilizers. If they were really selective for serotonin, they just wouldn't be antidepressants. And chemicals that antagonize serotonin do seem to function as antidepressants (Martin, et al., 1992). When an SSRI is used to treat irritability and aggression, it is appropriate to call it a tranquilizer. When drugs are used empirically, without really understanding the disease or the drug, classifications, descriptions, and names are subjective. The serotonin situation reminds me of the history of DES: For almost twenty years, this synthetic estrogen was marketed for the prevention of abortions; then it came out as the "morning after" contraception/abortion pill. "If increasing serotonin isn't the cure, then maybe decreasing serotonin will be the cure."

To begin to understand serotonin, it's necessary to step back from the culture of neurotransmitters, and to look at the larger biological picture.

Serotonin and estrogen have many systematically interrelated functions, and women are much more likely to suffer from depression than men are. Serotonin and histamine are increased by estrogen, and their activation mimics the effects of estrogen. Serotonin is closely involved in mood disorders, but also in a great variety of other problems that affect women much more frequently than men. These are probably primarily energy disorders, relating to cellular respiration and thyroid function. Liver disease and brain disease, e.g., Alzheimer's disease, are both much more common in women than in men, and serotonin and estrogen strongly affect the energetic processes in these organs. Liver disease can increase the brain's exposure to serotonin, ammonia, and histamine. It isn't just a coincidence that these three amines occur together and are neurotoxic; they are all stress-related substances, with natural roles in signaling and regulation.

There are good reasons for thinking that serotonin contributes to the nerve damage seen in multiple sclerosis and Alzheimer's disease.

The high incidence of multiple sclerosis in women, and its onset during their reproductive years, is well known. The number of brain lesions is associated with the ratio of estrogen to progesterone. Estrogen activates mast cells to release histamine and serotonin, and activated mast cells can produce brain edema and demyelination. Blood clots have been microscopically associated with brain lesions like those in multiple sclerosis, and the platelets in clots release neurotoxic serotonin.

In Parkinson's disease, the benefits seen from increasing the concentration of dopamine could result from dopamine's antagonism to serotonin; anti-serotonin drugs can alleviate the symptoms, and 5-hydroxytryptophan can worsen the symptoms (Chase, et al., 1976). Other movement disorders, including akathisia and chorea, can be produced by serotonin. In autism, repetitive motions are a common symptom, and serotonin is high in the blood serum and platelets of autistic children and their relatives. Irritable bowel syndrome, another kind of "movement disorder," can be treated effectively with anti-serotonin agents. This syndrome is very common in women, with premenstrual exacerbations, when estrogen is highest. One of the side effects of oral contraceptives is chorea, uncontrollable dancing movements. Some research has found increased serotonin in people with Huntington's chorea (Kish, et al., 1987), and positive results with bromocriptine have been reported (Agnoli, et al., 1977).

The neurosteroid, allopregnanolone, for which progesterone is the precursor, facilitates the inhibitory action of GABA, which is known to be deficient in some disorders of mood and movement. This suggests that progesterone will be therapeutic in the movement disorders, as it is in various mood problems. Progesterone has some specific antiserotonin actions (e.g., Wu, et al., 2000).

The "serotonin reuptake inhibitors" "are presumed" to have the same effect on the brain that they have on blood platelets. They inhibit the ability of platelets to retain and concentrate serotonin, allowing it to stay in the plasma. This uptake-inhibited condition is a model of the platelet behavior seen in multiple sclerosis and Alzheimer's disease.

Serotonin and its derivative, melatonin, are both involved in the biology of torpor and hibernation. Serotonin inhibits mitochondrial respiration. Excitoxic death of nerve cells involves both the limitation of energy production, and increased cellular activation. Serotonin has both of these actions.

In hibernating animals, the stress of a declining food supply causes increased serotonin production. In humans and animals that don't hibernate, the stress of winter causes very similar changes. Serotonin lowers temperature by decreasing the metabolic rate. Tryptophan and melatonin are also hypothermic. In the winter, more thyroid is needed to maintain a normal rate of metabolism.

Increased serotonin interferes with the consolidation of learning. Hypothermia has a similar effect. Since estrogen increases serotonergia, and decreases body temperature, these effects help to explain the long-observed interference of estrogen with learning.

Although ammonia, produced by fatigue or liver inefficiency, creates torpor, it can also cause convulsions. It synergizes with serotonin, and both of these promote excitotoxicity.

Serotonin's other names include thrombotonin, thrombocytin, enteramine, and 5-HT, its chemical name (5-hydroxytryptamine). These historical names derive from its role in the intestine and in blood vessels. In 1951, it was discovered that enteramine and thrombotonin were a single substance, and its involvement in circulatory disease, especially hypertension and vascular spasms, was the focus of research. (The increase in the number of "cardiovascular events" recently seen in the study of women using estrogen is what might be expected from something which increases serotonin dominance.) It causes vasoconstriction and vasospasm, and promotes clotting, when it's released from platelets. Especially when it is released from mast cells, it is considered to be an inflammatory mediator, along with histamine. Edema, bronchoconstriction, immunosuppression, and joint swelling are produced by the release of serotonin from platelets or other cells. As inflammatory mediators, serotonin and histamine are directly involved in asthma, hives, gastrointestinal damage from alcohol, nerve cell damage, edema, and shock.

The broadly protective effects of antihistamine drugs have been energetically exploited by the drug industry for fifty years. Why haven't antiserotonin drugs been similarly emphasized?

Research on LSD and its derivatives led to drugs such as bromocriptine, which oppose the effects of histamine and estrogen. Some of bromocriptine's effects are clearly antagonistic to serotonin, though bromocriptine is usually called a "dopamine agonist"; dopamine is pretty generally a serotonin antagonist. Methysergide, a related drug with antiserotonin activity, is effective in protecting the brain from the effects of strokes. But there is a general disinclination to understand the broad biological meaning of these effects.

I think the corrupt campaign against LSD played a large role in this: If the therapeutic value of LSD and related drugs (e.g., methysergide) with expired patents,[†] used as antiserotonin agents, became widely known,

the existing system of power and profit would be threatened. The war on drugs has always had its ulterior motives,including justifying domestic and foreign interventions in issues that have nothing to do with drugs. And in the case of the serotonin/antiserotonin mythology, this "war" has been rewarding to the drug industry—Lilly makes over $2 billion annually on Prozac. Each suicide caused by Prozac would appear to be balanced by several hundred thousand dollars earned by the corporation. If the war on drugs were serious, this would be a good place to start. And in weighing what corporate punishments might be appropriate, this corporation's financial support for universal capital punishment should be taken into account. Many experiments have shown that estrogen is very important for aggressive behavior in animals, and estrogen promotes serotonin's actions. Some research shows that increased serotonin is associated with certain types of increased aggressiveness, and antiserotonin agents decrease aggressiveness (Ieni, et al., 1985; McMillen, et al., 1987) but the clearest research has to do with the crucial role of serotonin in learned helplessness. Learned helplessness is a biological condition that is created by inescapable stress. In this state, animals that would normally swim for hours will stop swimming after a few minutes and allow themselves to drown. They simply don't have enough mental or physical energy to overcome challenges.

In learned helplessness, the level of serotonin is high, and an excess of serotonin helps to create the state of learned helplessness.

Serotonin activates glycolysis, forming lactic acid. Excess lactic acid tends to decrease efficient energy production by interfering with mitochondrial respiration.

Heart failure, hypertension, muscle hyperalgesia (Babenko, et al., 2000), some panic reactions, and other maladaptive biological events associated with problems of energy metabolism, are promoted by excessive serotonin.

Autistic children and their relatives have high concentrations of serotonin in their serum and platelets. Members of a family tend to eat the same foods and to share other environmental conditions. Prenatal hypothyroidism and various kinds of imprinting, including hyperestrogenism, could account for this. Some studies have reported that thyroid supplements help autistic children, and anti-serotonin drugs have caused improvement in both children and adults.

Serotonin tends to cause hypoglycemia, and hypoglycemia inhibits the conversion of thyroxine into the active T_3 hormone. Hypoglycemia and hypothyroidism increase noradrenaline, and autistic people have been found to have more noradrenaline than normal. These changes, along with the general hypometabolism caused by excess serotonin, seem to justify the use of a thyroid supplement in autism and other serotonin-excess syndromes.

Overdose with the serotonin reuptake inhibitors, or with 5-hydroxytryptophan, which has effects similar to serotonin, can cause the sometimes fatal "serotonin syndrome." Symptoms can include tremors, altered consciousness, poor coordination, cardiovascular disturbances, and seizures. Treatment with anti-serotonin drugs can alleviate the symptoms and usually can prevent death.

The serotonin syndrome has been reported in users of St. John's wort as an antidepressant. Since the other large neutral amino acids compete with tryptophan for entry into cells, the branched chain amino acids have some anti-serotonin activity, and this could be a justification for their use by athletes, since tryptophan and serotonin decrease glycogen stores and reduce endurance.

The only amino acid that has ever been found to be carcinogenic is tryptophan. Its ability to mimic estrogen in promoting the release of prolactin is probably responsible.

A large carbohydrate meal increases the ratio of tryptophan to the competing amino acids, and it has been proposed that this can shift the body's balance toward increased serotonin. In an animal study, bromocriptine, which shifts the balance away from serotonin, reduced obesity and insulin and free fatty acids, and improved glucose tolerance.

All of these observations are easiest to understand in terms of the suppression of cellular energy. Serotonin, like estrogen, lowers cellular ATP and interferes with oxidative metabolism.

Serotonin, like histamine, has its proper physiological functions, but it is a mediator of stress that has to be systematically balanced by the systems that support high energy respiratory metabolism. The use of supplements of tryptophan, hydroxytryptophan, or of the serotonin promoting antidepressant drugs, seems to be biologically inappropriate.

Many of the symptoms produced by excess serotonin are also the symptoms of hypothyroidism. Thyroid, progesterone, and high quality protein nutrition are central to protection against the serotonin syn-

dromes. (Progesterone, like LSD, can inhibit the firing of serotonergic nerves, but an overdose, unlike LSD, never produces hallucinations.)

One of the many actions of the "SSRI" (such as fluoxetine, Prozac), which aren't related to their effect on serotonin, is to increase the concentration of allopregnanolone in the brain, imitating the action of increased progesterone. Following this discovery, Lilly got Prozac approved as a treatment for premenstrual syndrome. Since the production of allopregnanolone and progesterone depends on the availability of pregnenolone and cholesterol, a low cholesterol level would be one of the factors making this an inappropriate way to treat PMS.

If we think biologically, starting with the role of serotonin as a damage-induced inflammatory mediator, we can speculate that an infinite number of irritating substances will be "serotonin reuptake inhibitors." The particular history of the "third generation antidepressants" is one that should disturb our tranquility.

† I don't want to imply that the receptor theory is wrong just because it allows for the introduction of innumerable experimental artifacts; it is primarily wrong because it is tied to the profoundly irrelevant "membrane theory" of cell regulation.

† Preparation for Lysergic Acid Amides: United States Patent Office 2,736,728 Patented February 28, 1956 Richard P. Pioch, Indianapolis, Indiana, assignor, to Eli Lilly and Co., Indianapolis, Indiana, a corporation of Indiana. No drawing. Application December 6, 1954, Serial No. 473,443. 10 claims. (Cl. 260–285.5)
From the PDR on Prozac: "Pharmacodynamics: The antidepressant and antiobsessive-compulsive action of fluoxetine is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine."

Serotonin

Effects in Disease, Aging and Inflammation

Ray Peat's Newsletter, 2015

INTERPRETING medical publications requires some skills that aren't needed for understanding more strictly scientific reports, because medical writing often takes into account the fact that physicians spend most of their time interacting with the public, rather than studying. The public's understanding of medicine is shaped by "public relations," by the introduction of words and concepts that frame the argument. (The linguist George Lakoff summarized the essence of public relations by observing that people reject facts that are outside their view of reality, their mental framework.) Television and public schools now frame the worldview of the affluent cultures, according to the needs of the ruling powers. Long before specific prescription drugs could be advertised directly to consumers, the medical and pharmaceutical industries were creating a favorable frame for their products.

Many years ago, public relations experts used expensive opinion polls to judge the effectiveness of their efforts, but now there is a convenient way to see how the general public is thinking: Wikipedia, the internet encyclopedia. The success of corporate advertising can be seen in their recent article on serotonin, which says "It is a well-known contributor to feelings of well-being; therefore it is also known as a 'happiness hormone' despite not being a hormone."

The culture that has happy and unhappy hormones was a culture in which each hormone had a receptor, a substance in a cell which, when its ligand was bound to it, made the cell do something. Although that culture still has influence in the 21st century, discoveries made between 1940 and 1970 showed that those mechanical ideas of receptors didn't reflect biological reality. Albert Szent-Györgi and the Pullmans showed that the electronic qualities of molecules determined their functions, and Szent-Györgyi showed that the state of the cell, tissue, and organism governed the effect of hormones and drugs. In the 1960s, substances with very different biological effects, such as acetylcholine and adrenaline, were shown to be selectively bound to the same cellular site in some cells. It was primarily the drug industry that created and sustained the specific receptor doctrine. That doctrine suited the recognition of their

public relations marketing experts, that successful advertising had to be directed at the sixth-grade educational level. The ideas of bioelectronics and context-sensitive molecules, like morphogenetic fields, were just too complicated to sell well.

Although metaphorical thinking can be creative and productive, metaphors mustn't be taken literally. The identification of multiple types of receptor for a given natural substance involves the use of different substances as metaphors or similes for the natural substance. That type of pharmacology is slowly being replaced by an attempt to understand state-dependent sensitivities. The energetic state of a cell, and of the whole organism, determines the meaning of events and conditions, such as the presence of the "regulatory substances."

The receptor culture can be tentatively disregarded when thinking about the history of serotonin. In the 1930s Vittorio Erspamer identified an amine in the intestine, that caused the intestine to contract. Then a group in England extracted an amine from serum that caused blood vessels to contract, and identified its chemical nature. Later, Erspamer showed that the intestinal amine and the vascular amine were chemically the same. The English group who had identified the substance by extracting tons of beef blood, wanted to find sensitive ways to assay it for further studies, and in 1951 they gave a sample to a pharmacologist, John Gaddum, who tested its effects on tissues including blood vessels and rat uteruses.

Gaddum tested the serotonin in combination with a variety of other drugs, including ergot derivatives, that he knew acted on smooth muscles, and very soon observed that LSD blocked the effects of serotonin. Since he knew that LSD produced mental effects (Sandoz had distributed samples of it to researchers in 1947), he reasoned that the brain might also contain serotonin, and by 1952 was able to demonstrate that it does contain small amounts of it. A couple of years later he suggested "that the mental effects of lysergic acid diethylamide are due to interference with the normal action of this HT (5-hydroxytryptamine, serotonin)." At the Rockefeller Institute in New York, Woolley and Shaw also saw the antagonistic effects on smooth muscle, and drew similar conclusions about the brain. Erspamer (Renic. sc. farmital. 1, 1, 1954) showed that LSD was a highly effective antagonist against the antidiuresis caused by serotonin (enteramine).

Around the same time, in the early 1950s, several people recognized that the symptoms produced by administering an excess of serotonin were similar to those experienced by people with intestinal tumors called argentaffinomas or carcinoid tumors, which are usually in the small intestine or appendix. The normal intestine contains about 95 % of the serotonin in the body (and the brain normally contains only about 1 %), and in the normal person only about 1 % of the dietary tryptophan is converted to serotonin. But in an advanced case of carcinoid, 60 % of the tryptophan can be turned into serotonin. Especially if the tumor has invaded the liver, the serotonin won't be destroyed by the liver in the usual way, and will circulate in the bloodstream at high levels, producing symptoms of flushing, sweating (sometimes dark-colored), diarrhea (serotonin stimulates small intestine smooth muscle, but inhibits the large[1]), nausea, anxiety, reduced urination, muscle and joint pains, and, in late stages, very often cardiovascular disease (especially inflammation, fibroma and calcification of the valves in the right side of the heart) and aggressive behavior[2] and psychosis.

Testing Gaddum's idea of antagonism between LSD and serotonin in humans, Montanari and Tonini found that intramuscular injections of serotonin antagonized the psychological effects of LSD. Other drugs, especially other ergot derivatives, were more successful than LSD in blocking the effects of serotonin.[3] There have been suggestions that pregnancy hormones could control serotonin excess.[4] Since estrogen promotes serotonin, progesterone is likely to be the protective factor.[5–7]

More recently,[8] it was found that LSD binding to a presumed serotonin receptor was low in carcinoid patients, supporting the idea of antagonism between the substances, but in the older studies symptoms, rather than competition for binding to certain proteins, were the focus of attention. The effects produced by injections and oral doses of synthetic serotonin, and of substances that block the synthesis of serotonin, were studied in both animals and humans. When a symptom such as clotting, flushing, or diarrhea is produced by serotonin itself, or prevented by a blocker of serotonin synthesis, "receptors" aren't an issue.

Aldous Huxley was one of the first people to think about the general biological meaning of drugs such as LSD. Referring to the ideas of Henri Bergson and William Blake, he suggested that the brain usually acts as a filter, or "reducing valve," to make us disregard most of the information we are receiving through our senses, and that the psychedelic drugs tem-

porarily remove the filter, or open the sensory reducing valve. Bergson had suggested that the filter was a practical measure needed to allow us to focus on practical survival needs; Blake had suggested that the doors of perception were kept closed for cultural reasons.

Some recent reviews have discussed the evidence supporting the serotonin system as primarily inhibitory and protective.[9,10] Goodman describes the serotonergic system as one of our "diffuse neuroregulatory systems," and suggests that drugs such as LSD weaken its inhibitory, filtering effect. (By changes in the effects of serotonin in the brain, produced by things that affect its synthesis, release, catabolism, or receptor action.[11,12]) LSD depresses the rate of firing of serotonergic nerves in the raphe nuclei[13] causing arousal similar to stimulation of the reticular formation, as if by facilitating sensory input into the reticular formation.[14]

In European culture, some people—e.g., Plato, Descarte, Locke, Eccles, probably even B.F. Skinner—have believed that mind and body are essentially different things (analogous to computer hardware and its programs), while another tradition—Blake, Lamarck, Darwin, C.L. Morgan, Pavlov, Reich, C.R. Cloninger, for example—has emphasized the continuity of consciousness and character with the body.

Understanding the authoritarian personality has been an important issue in the 20th century. Wilhelm Reich used some old ideas about the nervous system that were current near the beginning of the century, and Cloninger[15] and others,[16–18] toward the end of the century, were able to incorporate the newer information about the serotonergic-dopaminergic antagonisms. In this newer view, high serotonin production causes behavioral inhibition and harm avoidance, which are traits of the authoritarian personality, while anti-authorians tend to have "novelty seeking" personalities, with high dopamine and low serotonin functions.

In the 1960s, experimenters put electrodes into a chicken's optic nerve, and when the chicken saw a checkerboard pattern, they could measure a patterned electrical activity in the nerve. Without the light stimulating the retina, the nerve was quiet. But when they gave the chicken LSD or similar chemicals, they recorded patterned electrical activity in the nerve, in the absence of external stimulation. Around the same time, other experimenters showed that retinal fatigue quickly desensitized the retina, preventing the transmission of impulses to the brain, except when the light pattern corresponded to something familiar,

showing that impulses from the brain are always involved in renewing, in patterned ways, the sensitivity of the retina.

The latter experiment shows that everyone's perception involves an outward-directed activity of the brain, and the experiments using the chemical stimulants suggested that the intensity of the outward- directed action can vary.

The inhibitory serotonergic "harm avoidance" system, and the opposing excitatory activating "novelty seeking" systems are constantly being influenced by many factors, including nutrition, hormones, environmental challenges and opportunities, social interactions, seasons, and the rhythm of night and day alternation.

Several kinds of research are now showing that the effects of the environment on the serotonergic system and its antagonists can influence every aspect of health, not just the personality.

For example, there have been suggestions that early life isolation of an animal can affect its serotonergic activity and increase its anxiety, aggression, or susceptibility to stress,[19–21] and these effects are associated with increased risk of becoming depressed, and developing organic problems. Animals kept in darkness (or with blurring lenses) become nearsighted, as the eyeball grows longer under the influence of increased serotonin, and the eyes are protected against myopia by serotonin antagonists.[22] The incidence of myopia is increasing, at least in countries with industrialized economies, and is more common in females.

Migraine headaches are also increasing in incidence. By the end of the 1950s, it was widely accepted that migraine headaches and associated symptoms including nausea and visual disturbances were caused by an excess of serotonin, and antiserotonin drugs of various types were being used for treatment. In one of the early studies of the use of LSD in psychotherapy, some of the patients noticed that their chronic headaches had stopped. Cluster headaches have also responded well to LSD and similar drugs.[23]

Women have migraines more often than men do, and they tend to occur in association with ovulation or menstruation. Estrogen inhibits monoamino oxidase, MAO, especially the A form that is most active in detoxifying serotonin, and it increases the enzymes that control the rate of serotonin synthesis. During serotonin excess, the veins and capillaries of the pia mater are engorged with blood, while circulation to the brain generally is depressed. Visual symptoms are probably produced

by constriction of arterioles, while the pain is associated with engorged veins. Progesterone activates the MAO-A, and has other antiserotonin effects on blood vessels and nerves.

Recently,[24,25] females have been found to be more susceptible to stress, and to have reduced uptake of serotonin (prolonging its effects), which increases glucocorticoids and ACTH.Kendler, et al.[26] have found that people with reduced serotonin uptake are more susceptible to stress-induced depression.

The increase of inhibitory serotonin with stress and depression is probably biologically related to the role of serotonin in hibernation, which is an extreme example of "harm avoidance" by withdrawal. A diet high in polyunsaturated fat increases the tendency to go into hibernation, probably by increasing the brain's uptake of tryptophan. When this is combined with an increasingly cold environment, the form of MAO that removes serotonin decreases its activity, while the form that removes norepinephrine increases its activity. The metabolite of serotonin, 5-HIAA, decreases, as the effect of serotonin increases.

In experiments to investigate the mechanism of hibernation, animals were injected with serotonin, at different environmental temperatures. In a cool environment, the serotonin caused their temperature to fall, by decreasing their heat production, and increasing their loss of heat (by causing vasodilation in the skin, "flushing"). In a hot environment, serotonin can cause the animal's temperature to rise.

Serotonin can reduce the production of energy by inhibiting mitochondrial respiratory enzymes,[27] and by reduction of oxygen delivery to tissues by vasoconstriction. It also appears to interfere with the use of glucose.[28,29]

The brains of people with Alzheimer's disease have a decreased ability to metabolize glucose, and high cortisol contributes to the altered glucose metabolism, and to the destruction of nerve cells. People with Cloninger's "harm avoidance" personality trait, which is closely associated with serotonin,[30] are more likely to develop dementia.[31] These observations are consistent with the stress-susceptibility of people with high serotonin exposure, and to the effects of cortisol on nerves and glucose-derived energy production.

Researchers in Brasil have suggested that the serotonergic system facilitates conditioned fear, while inhibiting the fight or flight reaction, and that this can protectively limit the stress response.[32] "5HT systems

reduce the impact of impending or actual aversive events. Anticipation of an aversive event is associated with anxiety and this motivates avoidance behaviour".[33] In a stressful situation, the serotonergic nerves can prevent ulcers. In other contexts, though, increased serotonin can cause ulcers.

The protective, defensive reactions involving serotonin's blocking of certain types of reaction to ordinary stresses, are similar to the effects of serotonin in hibernation and in Alzheimer's disease.[34–36] In those extreme conditions, serotonin reduces energy expenditure, eliminating all brain functions except those needed for simple survival. These parallels suggest that improving energy production, for example by providing ketones as an alternative energy source, while reducing the stress hormones, might be able to replace the defensive reactions with restorative adaptive nerve processes, preventing or reversing Alzheimer's disease.

One of the factors promoting excess cortisol production is intestinal irritation, causing absorption of endotoxin and serotonin. Fermentable fibers (including pectins and fructooligosaccharides) support the formation of bacterial toxins, and can cause animals to become anxious and aggressive. Fed to horses, some types of fiber increase the amount of serotonin circulating in the blood. Grains, beans, and other seeds contain fermentable fibers that can promote intestinal irritation.

The liver has several ways to detoxify endotoxin and serotonin, but these can fail as a result of poor nutrition and hypothyroidism.

The lung can bind and destroy any excess serotonin that reaches it. A lack of carbon dioxide makes platelets release their stored serotonin, and it probably has the same effect in the lung endothelial cells. Without being able to bind the serotonin, the enzyme (indoleamine 2,3-dioxygenase) would be unable to destroy it.

An excess of tryptophan in the diet, especially with deficiencies of other nutrients, can combine with inflammation to increase serotonin. Polyunsaturated fatty acids promote the absorption of tryptophan by the brain, and its conversion to serotonin. (A "deficiency" of polyunsaturated fat decreases the expression of the enzyme that synthesizes serotonin.[37]

Some fruits, including bananas, pineapples, and tomatoes, contain enough serotonin to produce physiological effects in susceptible people.

Besides avoiding foods containing fermentable fibers and starches that resist quick digestion, eating fibrous foods that contain antibacterial chemicals, such as bamboo shoots or raw carrots, helps to reduce

endotoxin and serotonin. Activated charcoal can absorb many toxins, including bacterial endotoxin, so it is likely to reduce serotonin absorption from the intestine. Since it can also bind or destroy vitamins, it should be used only intermittently. Frolkis, et al. (1989, 1984) found that it extended median and average lifespan of rats, beginning in old age (28 months) by 43 % and 34 %, respectively, when given in large quantities (equivalent to about a cup per day for humans) for ten days of each month.

The amino acid theanine, found in tea, has been reported to decrease the amount of serotonin in the brain, probably by decreasing its synthesis and increasing its degradation.

This seems to be the opposite of the processes in hibernation. Progesterone, thyroid, and niacinamide (not nicotinic acid or inositol hexanicotinate) are other safe substances that help to reduce serotonin formation, and/or accelerate its elimination. (Niacinamide seems to increase serotonin uptake.)

To provide usable energy to the over-stressed brain (and heart), R.L. Veech has advocated the use of ketones, but the pure chemicals are expensive to make. An easily available and inexpensive source of ketones (in the form of ketoacids, which can be converted to amino acids if they aren't needed for energy) is the juice extracted (with a centrifugal juicer) from raw potatoes, which also contains proteins and other nutrients. The juice can be scrambled like eggs, and is usually tolerated even by very debilitated people.

Hypothyroidism is a very common cause of increased serotonin,[38] and if the thyroid hormone is supplemented until symptoms are resolved, it's likely that the serotonin will have been normalized.

Stem Cells, Cell Culture, and Culture

Issues in Regeneration

Ray Peat's Newsletter, 2007

CELL renewal is a factor in all aspects of health and disease, not just in aging and the degenerative diseases. Many people are doing valid research relating to cell renewal and regeneration, but its usefulness is seriously limited by cultural and commercial constraints. By recovering some of our suppressed traditional culture, I think regenerative therapies can be developed quickly, by identifying and eliminating as far as possible the main factors that interfere with tissue renewal.

Science grew up in the highly authoritarian cultures of Western Europe, and even as it contributed to cultural change, it kept an authoritarian mystique. Any culture functions as a system of definitions of reality and the limits of possibility, and to a great extent the "laws of nature" are decreed so that they will harmonize with the recognized laws of society.

The practical success of Newton's "laws" of motion when they were applied to ballistics and "rocket science" has led many people to value calculation, based on those laws, over evidence. In biology, the idea that an organism is "the information it contains in its DNA blueprint" is an extension of this. The organism is turned into something like a deductive expression of the law of DNA. This attitude has been disastrous.

The old feudal idea of a divine and stable social organization was applied by some people to their idea of biological organization, in which each cell (ruled by its nucleus) had its ordained place in the organism, with the brain and the "master gland," the pituitary, ruling the subordinate organs, tissues, and cells. "Anatomy" was taught from dead specimens, microscope slides, and illustrations in books. Most biologists' thoughts about cells in organisms reflect the static imagery of their instruction. ("The histological image of these tissues actually reflects an instantaneous picture of cells in a continuous flux."[1])

When a person has playful and observant interactions with natural things, both regularities and irregularities will be noticed, and in trying to understand those events, the richness of the experience will suggest an expansive range of possibilities. Perception and experimentation lead to understandings that are independent of culture and tradition.

But the mystique of science easily imposes itself, and distracts our attention from direct interactions with things. As we learn to operate lab instruments, we are taught the kinds of results that can be expected, and the concepts that will explain and predict the results of our operations. Science, as we learn about it in schools and the mass media, is mostly a set of catechisms.

Our theories about organisms inform our experiments with cells or tissues that have been isolated from those organisms. The conditions for growing cells in dishes are thought of as "physiological," in relation to the solution's "physiological osmolarity," "physiological pH," nutrients, oxygenation, temperature, pressure, etc. But these concepts of what is physiological derive from the monolithic ideology of the doctrinaire, and often fraudulent, mainstream of biological science.

The catechismic nature of science has led people to expect some "break-throughs" to occur in certain areas, and as authoritarian science has grown into "big science" managed by corporations and governments, those break-throughs are generally expected to be produced by the newest and most expensive developments of "high technology."

But looking closely at the real events and processes in the sciences in the last couple of centuries, it turns out that useful advances have been produced mainly by breaking away from authoritarian doctrines, to return to common sense and relatively simple direct observations.

Although people were cloning animals in the 1960s, it was still widely taught that it was impossible. The students of the professors who taught that it was impossible are now saying that it requires high technology and new research.

For the last 100 years the most authoritative view in biology has been that there are no stem cells in adults, that brains, hearts, pancreases and oocytes are absolutely incapable of regeneration. But now, people seem to be finding stem cells wherever they look, but there is a mystique of high technology involved in finding and using them.

Whether it's deliberate or not, the emphasis on stem cell technology has the function of directing attention away from traditional knowledge, the way allopathic medicine has de-emphasized the intrinsic ability of people to recover from disease.

This resembles the way that the Mendel-Morgan gene doctrine was used to suppress the knowledge gained from centuries of experience of plant and animal breeders, and to belittle the discoveries of Luther

Burbank, Paul Kammerer, Trofim Lysenko, and Barbara McClintock. The same type of biochemical process that caused the hereditary changes those researchers studied are involved in the differentiation and dedifferentiation of stem cells that regulate healing and regeneration.

In the 1940s, even children discussed the biological discoveries of the 1920s and 1930s, the work in regeneration and adaptation, parthenogenesis, and immortalization. The ideas of J. Loeb, T. Boveri, A. Gurwitsch, J. Needham, C.M. Child, A. Carrel, et al., had become part of the general culture.

But that real biology was killed by a consortium of industry and government that began a little before the second world war. In 1940, the government was supporting research in chemical and biological warfare, and with the Manhattan Project the role of government became so large that all of the major research universities were affected. Shortly after the war, many researchers from the Manhattan Project were redeployed into "molecular genetics," where the engineering attitude was applied to organisms.

The simplistic genetic dogmas were compatible with the reductionist engineering approach to the organism. The role of the government assured that the universities would subscribe to the basic scientific agenda. The atmosphere of that time was described by Carl Lindegren as *The Cold War in Biology* (1966).

The disappearance of the field concept in developmental biology was one of the strangest events in the history of science. It didn't just fade away, it was "disappeared," in a massive undertaking of social engineering. In its absence, stem cells will seem to be a profitable technological marvel, rather than a universal life function, with a central role in everything we are and everything we do and can become.

Many people have tried to explain aging as a loss of cells, resulting from an intrinsic inability of any cell other than a germ cell to multiply more than a certain number of times. More than 40 years ago Leonard Hayflick popularized this doctrine in its most extreme form, saying that no cell can divide more than 50 times unless it is converted into a cancer cell. He and his followers claimed that they had explained why organisms must age and die. At the moment the ovum is fertilized, the clock starts ticking for the essentially mortal somatic cells.

In 1970, it was being seriously proposed that memory was produced by the death of brain cells, in a manner analogous to the holes punched

in cards to enter data into computers. The cultural dogma made it impossible to consider that learning could be associated with the birth of new cells in the adult brain.

With the announcement in 1997 of the cloning of the sheep Dolly from a somatic cell taken from a 6 year old sheep, there was renewed interest in the idea made famous by Alexis Carrel that all cells are potentially immortal, and in the possibility of preserving the vitality of human cells. Within a few months, Hayflick began reminding the public that "In the early 1960's we overthrew this dogma after finding that normal cells do have a finite replicative capacity." ("During the first half of this century it was believed that because cultured normal cells were immortal, aging must be caused by extra-cellular events.") The way Hayflick "overthrew" more than 35 years of work at the Rockefeller Institute was by growing one type of cell, a lung fibroblast, in culture dishes, and finding that the cultures deteriorated quickly.

To draw global conclusions about an organism's development and aging from the degenerative processes seen in a single type of cell, grown in isolation from all normal stimuli, would have been treated as nothing but wild speculation, except that it occurred within a culture that needed it. No aspect of Hayflick's cell culture system could properly be called physiological.

Other researchers, simply by changing a single factor, caused great increases in the longevity of the cultured cells. Simply using a lower, more natural oxygen concentration, the cells were able to undergo 20 more divisions. Just by adding niacin, 30 more divisions; vitamin E, 70 more divisions. Excess oxygen is a poison requiring constant adaptation.

Hayflick also published the observation that, while the cells kept in dishes at approximately body temperature deteriorated, cells kept frozen in liquid nitrogen didn't deteriorate, and he concluded that "time" wasn't the cause of aging. When I read his comments about the frozen cells, I wondered how anyone of normal intelligence could make such stupid statements. Since then, facts that came out because of the Freedom of Information Act, cause me to believe that a financial motive guided his thoughts about his cultured fibroblasts.

Hayflick and his followers have been attacking the idea of anti-aging medicine as quackery. But he is closely involved with the Geron corporation, which proposes that genetic alterations relating to telomeres may

be able to cure cancer and prevent aging. Their claims were reported by CNN as "Scientists discover cellular 'fountain of youth.'"

The "wear and tear" doctrine of aging that derived from the ideology of the gene was reinforced and renewed by Hayflick's cell culture observations, and it continued to rule the universities and popular culture.

But detailed investigation of skin cell growth showed that cells in the lower layer of the skin divide at least 10,000 times in a normal lifetime, and similar processes occur in the lining of the intestine. The endometrium and other highly renewable tissues just as obviously violated Hayflick's limit. Transplantation experiments showed that pieces of mammary tissue or skin tissue could survive through ten normal lifetimes of experimental animals without suffering the effects of aging.

Even the liver and adrenal gland are now known to be continuously renewed by "cell streaming," though at a slower rate than the skin, conjunctiva, and intestine. Neurogenesis in the brain is now not only widely accepted, it is even proposed as a mechanism to explain the therapeutic effects of antidepressants.[2]

August Weismann's most influential doctrine said that "somatic cells are mortal, only the germline cells are immortal," but he based the doctrine on his mistaken belief that only the "germline" cells contained all the genes of the organism. In 1885, to "refute" Darwin's belief that acquired traits could be inherited, he promulgated an absolute "barrier" between "germline" and "soma," and invented facts to show that hereditary information can flow only from the germline to the somatic cells, and not the other direction. Shortly after DNA became popular in the 1950s as "the genetic material," Weismann's barrier was restated as the Central Dogma of molecular genetics, that information flows only from DNA to RNA to protein, and never the other direction.

It was only in 2003, after the reality of cloning was widely recognized, that a few experimenters began to investigate the origin of "germline" cells in the ovary, and to discover that they derive from somatic cells.[3] With this discovery, the ancient knowledge that a twig (*klon*, in Greek) cut from a tree could grow into a whole tree, bearing fruit and viable seeds, was readmitted to general biology, and the Weismann barrier was seen to be an illusion.

Millions of people have "explained" female reproductive aging as the consequence of the ovary "running out of eggs." Innumerable publications purported to show the exact ways in which that process occurs,

following the Weismann doctrine. But now that it is clear that adult ovaries can give birth to new oocytes, a new explanation for female reproductive aging is needed. It is likely that the same factors that cause female reproductive aging also cause aging of other systems and organs and tissues, and that those factors are extrinsic to the cells themselves, as Alexis Carrel and others demonstrated long ago. This is a way of saying that all cells are potential stem cells. The "niche" in which new cells are born in the streaming organism, and the processes by which damaged cells are removed, are physiological issues that can be illuminated by the idea of a morphogenetic field.

When the post-war genetic engineers took over biological research, the idea of a biophysical field was totally abandoned, but after about 15 years, it became necessary to think of problems beyond those existing within a single bacterium, namely, the problem of how an ovum becomes and embryo. Francis Crick, of DNA fame, who was educated as a physicist, revived (without a meaningful historical context) the idea of a diffusion gradient as a simple integrating factor that wouldn't be too offensive to the reductionists. But for events far beyond the scale of the egg's internal structure, for example to explain how a nerve axon can travel a very long distance to innervate exactly the right kind of cell, the diffusion of molecules loses its simplicity and plausibility. (Early in the history of experimental embryology, it was observed that electrical fields affect the direction of growth of nerve fibers.)

C. M. Child saw a gradient of metabolic activity as an essential component of the morphogenetic field. This kind of gradient doesn't deny the existence of diffusion gradients, or other physical components of a field. Electrical and osmotic (and electro-osmotic) events are generated by metabolism, and affect other factors, including pH, oxidation and reduction, cell motility and cell shape, ionic selectivity and other types of cellular selectivity and specificity. Gradients of DNA methylation exist, and affect the expression of inherited information.

Methylation decreases the expression of particular genes, and during the differentiation of cells in the development of an embryo, genes are methylated and demethylated as the cell adapts to produce the proteins that are involved in the structure and function of a particular tissue. Methylation (which increases a molecule's affinity for fats) is a widespread process in cells, and for example regulates cellular excitability. It is affected by diet and a variety of stresses.

DNA methylation patterns are normally fairly stable, and can help to account for the transgenerational transmission of acquired adaptations, and for neonatal imprinting that can last a lifetime. But with injury, stress, and aging, the methylation patterns of differentiated tissues can be changed, contributing to the development of tumors, or to the loss of cellular functions. Even learning can change the methylation of specific genes. During *in vitro* culture, the enzymes of gene methylation are known to be increased, relative to their normal activity.[4]

The phenomenon of "gene" methylation in response to environmental and metabolic conditions may eventually lead to the extinction of the doctrine that "cells are controlled by their genes."

During successful adaptation to stress, cells make adjustments to their metabolic systems (for example with a holistic change of the degree of phosphorylation, which increases molecules' affinity for water), and their metabolic processes can contribute to changes in their state of differentiation. Some changes may lead to successful adaptation (for example by producing biogenic stimulators that stimulate cell functioning and regeneration), others to failed adaptation. Even the decomposition of cells can release substances that contribute to the adaptation of surrounding cells, for example when sphingosines stimulate the production of stem cells.

DNA methylation is just one relatively stable event that occurs in relation to a metabolic field. Modifications of histones (regulatory proteins in chromosomes, which are acetylated as well as methylated) and structural-contractile filaments also contribute to the differentiation of cells, but the pattern of DNA methylation seems to guide the methylation of histones and the structure of the chromosomes.[5]

Steroids and phospholipids, neurotransmitters and endorphins, ATP, GTP, other phosphates, retinoids, NO and CO_2—many materials and processes participate in the coherence of the living state, the living substance. Carbon dioxide, for example, by binding to lysine amino groups in the histones, will influence their methylation. Carbon dioxide is likely to affect other amino groups in the chromosomes.

The number and arrangement of mitochondria is an important factor in producing and maintaining the metabolic gradients. Things that decrease mitochondrial energy production—nitric oxide, histamine, cytokines, cortisol—increase DNA methylation. Decreased gene expression is associated with reduced respiratory energy. It seems reasonable

to guess that increased gene expression would demand increased availability of energy.

As an ovum differentiates into an organism, cells become progressively more specialized, inhibiting the expression of many genes. Less energy is needed by stably functioning cells, than by actively adapting cells. A.I. Zotin described the process of maturing and differentiating as a decrease of entropy, an increase of order accompanying a decreased energy expenditure. The entropic egg develops into a less entropic embryo with a great expenditure of energy.

The partially differentiated stem cell doesn't go through all the stages of development, but it does expend energy intensely as it matures.

The restoration of energy is one requirement for the activation of regeneration. When a hormone such as noradrenaline or insulin causes a stem cell to differentiate *in vitro*, it causes new mitochondria to form. This is somewhat analogous to the insertion of mitochondria into the ripening oocyte, by the nurse cells that surround it. The conditionally decreased entropy of maturation is reversed, and when sufficient respiratory energy is available, the renewed and refreshed cell will be able to renew an appropriate degree of differentiation.

When simple organisms, such as bacteria, fungi, or protozoa are stressed, for example by the absence of nutrients or the presence of toxins, they slow their metabolism, and suppress the expression of genes, increasing the methylation of DNA, to form resistant and quiescent spores. Our differentiated state doesn't go to the metabolic extreme seen in sporulation, but it's useful to look at maturity and aging in this context, because it suggests that the wrong kind of stress decreases the ability of the organism to adapt, by processes resembling those in the spore-forming organisms.

Charles Vacanti, who has grown cartilage from cells taken from 100 year old human cartilage, believes our tissues contain "spore cells," very small cells with slow metabolism and extreme resistance to heat, cold, and starvation.

If the slowed metabolism of aging, like that of sporulating cells, is produced by a certain kind of stress that lowers cellular energy and functions, it might be useful to think of the other stages of the stress reaction in relation to the production of stem cells. Selye divided stress into a first stage of shock, followed by a prolonged adaptation, which could sometimes end in exhaustion. If the maturity of differentiated

functioning is equivalent to the adaptation phase, and cellular decline and disintegration is the exhaustion phase, then the shock-like reaction would correspond to the birth of new stem cells.

Selye described estrogen's effects as equivalent to the shock-phase of stress. Estrogen's basic action is to make oxygen unavailable, lowering the oxygen tension of the tissues, locally and temporarily. Like nitric oxide, which is produced by estrogenic stimulation, estrogen interferes with energy production, so if its stimulation is prolonged, cells are damaged or killed, rather than being stimulated to regenerate.

Extrinsic factors elicit renewal, the way stress can elicit adaptation. While aging cells can't use the oxygen that is present, a scarcity of oxygen can serve as a stimulus to maximize the respiratory systems. Brief oxygen deprivation excites a cell, causes it to swell, and to begin to divide.

Oxygen deprivation, as in the normally hypoxic bone marrow, stimulates the formation of stem cells, as well as the biogenesis of mitochondria. As the newly formed cells, with abundant mitochondria, get adequate oxygen, they begin differentiation.

Form, based on cellular differentiation, follows function—a vein transplanted into an artery develops anatomically into an artery, a colon attached directly to the anus becomes a new rectum with its appropriate innervation, a broken bone restructures to form a normal bone. If the bladder is forced to function more than normal, by artificially keeping it filled, its thin wall of smooth muscle develops into a thick wall of striated muscle that rhythmically contracts, like the heart. If a tadpole is given a vegetarian diet, the absorptive surface of its digestive system will develop to be twice the size of those that are fed meat. Pressure, stretching, and pulsation are among the signals that guide cells' differentiation.

Very early in the study of embryology it was noticed that the presence of one tissue sometimes induced the differentiation of another kind, and also that there were factors in embryonic tissues that would stimulate cell division generally, and others that could inhibit the growth of a particular tissue type. Diffusable substances and light were among the factors identified as growth regulators.

Extracts of particular tissues were found to suppress the multiplication of cells in that type of tissue, in adult animals as well as in embryos. In the 1960s, the tissue-specific inhibitors were called chalones.

The brain's development is governed by the presence in the organism of the body part to which it corresponds, such as the eyes or legs. The

number of cells in a particular part of the nervous system is governed by the quantity of nervous input, sensory or motor, that it receives. An enriched environment causes a bigger brain to grow. Sensory nerve stimulation of a particular region of the brain causes nerve cells to migrate to that area (a process called neurobiotaxis[6]), but nerve stimulation also causes mitochondria to accumulate in stimulated areas. Nerve activity has a trophic, sustaining influence on other organs, as well as on the brain. Nerve stimulation, like mechanical pressure or stretching, is an important signal for cellular differentiation.

When stem cells or progenitor cells are called on to replace cells in an organ, they are said to be "recruited" by that organ, or to "home" to that organ, if they are coming from elsewhere. Traditionally, the bone marrow has been considered to be the source of circulating stem cells, but it now appears that a variety of other less differentiated cells can be recruited when needed. Cells from the blood can repair the endothelium of blood vessels, and endothelial cells can become mesenchymal cells, in the heart, for example.

The standard doctrine about cancer is that a tumor derives from a single mutant cell, but it has been known for a long time that different types of cell, such as phagocytes and mast cells, usually reside in tumors, and it is now becoming clear that tumors recruit cells, including apparently normal cells, from other parts of the same organ. For example, a brain tumor of glial cells, a glioma, recruits glial cells from surrounding areas of the brain, in a process that's analogous to the embryological movement of nerve cells to a center of excitation. Each tumor, in a sense, seems to be a center of excitation, and its fate seems to depend on the nature of the cells that respond to its signals.

To accommodate some of the newer facts about tumors, the cancer establishment has begun speaking of "the cancer stem cell" as the real villain, the origin of the tumor, while the bulk of the tumor is seen to be made up of defective cells that have a short life-span. But if we recognize that tumors are recruiting cells from beyond their boundaries, this process would account for the growth and survival of a tumor even while most of its cells are inert and dying, without invoking the invisible cancer stem cell. And this view, that it is the field which is defective rather than the cell, is consistent with the evidence which has been accumulating for 35 years that tumor cells, given the right environment, can differentiate into healthy cells.[7]

Simply stretching an organ[8] is stimulus enough to cause it to recruit cells from the bloodstream, and will probably stimulate multiplication in its local resident cells, too. Every "cancer field" probably begins as a healing process, and generally the healing and regeneration are at least partially successful.

When an organ—the brain, heart, liver, or a blood vessel—is inflamed or suffering from an insufficient blood supply, stem cells introduced into the blood will migrate specifically to that organ.

Organ specific materials (chalones) are known to circulate in the blood, inhibiting cell division in cells typical to that organ, but it also seems that organ specific materials are secreted by a damaged organ, that help to prepare stem cells for their migration into that organ. When undifferentiated cells are cultured with serum from a person with liver failure, they begin to differentiate into liver cells.

It is still common to speak of each organ as having a "clonal origin" in the differentiating embryo, as a simple expansion of a certain embryonic anlage. The implication of this way of thinking is that differentiation is determination in an irreversible sense. This is another case of medical ideas being based on images of fixed histological material. Normal cells, including nerve and muscle cells, can change type, with connective tissue cells becoming nerve cells, nerve cells becoming muscle and fiber cells, fat, fiber, and muscle cells redifferentiating, for example.

Cell movements in solid tissues aren't limited to the short distances between capillaries and the tissues nourished by those capillaries, rather, cells can migrate much greater distances, without entering the bloodstream. The speed of a single cell moving by ameboid motion can be measured by watching cells on a glass slide as they move toward food, or by watching cells of the slime mold Dictyostelium when they are aggregating, or by watching the pigment cells in and around moles or melanomas, under the influence of hormones. At body temperature, a single cell can crawl about an inch per day. Waves or spots of brown pigment can be seen migrating through the skin away from a mole, preceding the disintegration of the mole under the influence of progesterone or DHEA. Under ordinary conditions, pigment cells can sometimes be seen migrating into depigmented areas of skin, during the recovery of an area affected by vitiligo. These organized movements of masses of cells happen to be easy to see, but there is evidence that other types of cell can reconstruct tissues by their ameboid movements, when circumstances

are right. Tumors or tissue abnormalities can appear or disappear with a suddenness that seems impossible to people who have studied only fixed tissue preparations.

Stimulation is anabolic, building tissue, when the organism is adapting to the stimulation. Unused structures in cells and tissues are always being recycled by metabolic processes. When tissues are injured and become unable to function, some of their substances stimulate the growth of replacement cells.

Some types of injury or irritation can activate regenerative processes. A dermatology journal described the case of an old man who had been bald for many years who fell head-first into his fireplace. As his burned scalp healed, new hair grew. In the U.S., experimenters[9] have found that injuring the skin of mice stimulates the formation of stem cells that are able to become hair follicle cells, supporting the regeneration of cells that had been absent. A brief exposure to estrogen, and other stress related signals (nitric oxide, endorphin, prostaglandins) can initiate stem cell proliferation.

In the years after the first world war, Vladimir Filatov, who developed techniques of reconstructive surgery, including corneal transplants, found that cold storage of tissues (for example, corneas from cadavers) caused them to function better than fresh tissues, and he found that these stressed tissues would often spread a healing influence out into the surrounding tissues. Extracts of stressed tissues produced similar effects.

L.V. Polezhaev began studying the regenerative capacities of mammals in the late 1940s, and his work showed that processes similar to embryonic induction are involved in the organism's responses to damaged tissues. For example, when a piece of killed muscle tissue is enclosed in a capsule ("diffusion chamber") that permits molecules, but no cells, to diffuse through it, and implanted subcutaneously, it had no inductive effect on surrounding cells. But when the pores of the capsule allowed cells to enter, skeletal muscle formed where the dead tissue had been, and tissue resembling heart muscle formed outside the capsule. Phagocytosis had been essential for the induction to occur.

Macrophages are ordinarily thought of as "antigen-presenting cells" that help to activate the specific immune responses. But apparently phagocytosis is involved in the replacement of damaged tissues, by recruiting or inducing the differentiation of replacement cells. The

phagocytosis function isn't limited to the blood cells commonly called phagocytes; even nerve cells can ingest particles and fragments of damaged tissues.

Many factors regulate the process of phagocytosis. Stress and lipid peroxidation decrease phagocytosis,[10] and also damage mitochondria and inhibit cell renewal.

Unsaturated fatty acids inhibit phagocytosis,[11–14] and suppress mitochondrial function.[15] Dietary restriction activates phagocytosis,[16] suggesting that normal diets contain suppressive materials.

Subnormal temperatures cause a shift from phagocytosis to inflammation. Light, especially the red light which penetrates easily into tissues, activates the formation of new cells as well as their differentiation. It affects energy production, increasing the formation of mitochondria, and the activity of the DNA methyltransferase enzymes. Red light accelerates wound healing, and improves the quality of the scar, reducing the amount of fibrosis. The daily cycling between darkness and light is probably an important factor in regulating the birth and differentiation of cells.

Darkness suppresses mitochondrial function, and light activates it. Prolonged darkness increases cortisol, and cortisol (which makes cells more susceptible to excitotoxic death) inhibits stem cell proliferation.[17,18] Neurogenesis is suppressed by stress, and increased by spontaneous activity, and has a circadian rhythm. Aging and depression both involve a diminished ability to rhythmically lower the production of cortisol. Cell renewal requires a rhythmic decrease in the exposure to cortisol.

In the spring, with increased day length, the brains of song-birds grow, with an increased proliferation of cells in the part of the brain involved in singing. The production of progesterone increases in most animals in the spring, and it is the main hormone responsible for the birds' brain growth.

Progesterone and its metabolites protect brain cells against injury, and improve the brain's ability to recover after traumatic injury.[19] In the 1960s, Marion Diamond's group showed that environmental enrichment, or progesterone, caused brains to grow larger, and that these changes were passed on to descendants in a cumulative, increasing way. This suggests that the factors that promote neurogenesis also cause changes in the apparatus of reproduction and inheritance, that support the de-

velopment of the brain—probably including the methylation system, which is involved in regulating genes, and also mood and behavior.

Women's monthly cycles, in which a brief estrogen dominance is followed by sustained exposure to progesterone, are probably an important factor in the renewal of the cells of the brain and other organs, as well as those of the reproductive organs. The daily rhythms of hormones and metabolism are known to be involved in the regulation of cell renewal.

Environmental enrichment, learning, high altitude, and thyroid hormone promote the formation of new mitochondria, and stimulate stem cell proliferation. At least in some laboratories, 20 % oxygen, approximately the amount as in the atmosphere, suppresses the proliferation of stem cells.[20] This was the unphysiologically high concentration of oxygen used in Hayflick's cell cultures. At high altitudes, where tissues are exposed to less oxygen, and more carbon dioxide, there is a lower incidence of all the degenerative diseases, including cancer, heart disease, and dementia. Improved cellular energy production and more active renewal of cells would probably account for those differences.

For Crick, the idea of a diffusion gradient to explain embryonic development was simply an extension of his reductionist orientation, in which diffusing molecules induced or inhibited bacterial genes, and in which genes controlled cells. For people with that orientation, the adaptive mutations described by Carl Lindegren, and later by John Cairns, or even the stress-induced variability described by Lysenko, Strong, and McClintock, were heretical. Polezhaev's demonstration that cells could do something that molecular diffusion didn't do, threatened to take biology away from the reductionists. If the organism's adaptation to the environment involves changing its own genes, Crick's paradigm fails.

Crick's Central Dogma, derived from the ideology that produced Weismann's Barrier, has been invoked by generations of professors who wanted to deny the possibility of adaptive tissue renewal and regeneration. Without the dogma, new ideas about aging and disease will be needed. If somatic cells can adjust their genes, and if they can also differentiate into new eggs and sperms, new ideas about inheritance of acquired traits will be needed.

The replacement of injured cells means that mutations need not accumulate. Cell renewal with elimination of mutant cells has been observed in sun-damaged skin simply by stopping the damage, and mito-

chondria with damaged DNA can be replaced by healthy mitochondria simply by doing the right kind of exercise.

The regulation of cell renewal probably involves all of the processes of life, but there are a few simple, interacting factors that suppress renewal. The accumulation of polyunsaturated fats, interacting with a high concentration of oxygen, damages mitochondria, and causes a chronic excessive exposure to cortisol. With mitochondrial damage, cells are unable to produce the progesterone needed to oppose cortisol and to protect cells.

Choosing the right foods, the right atmosphere, the right mental and physical activities, and finding the optimal rhythms of light, darkness, and activity, can begin to alter the streaming renewal of cells in all the organs. Designing a more perfect environment is going to be much simpler than the schemes of the genetic engineers.

Sugar Issues

Ray Peat's Newsletter, 2012

Since the first doctor noticed, hundreds of years ago, that the urine of a diabetic patient tasted sweet, it has been common to call the condition the sugar disease, or sugar diabetes, and since nothing was known about physiological chemistry, it was commonly believed that eating too much sugar had to be the cause, since the ability of the body to convert the protein in tissues into sugar wasn't discovered until 1848, by Claude Bernard (who realized that diabetics lost more sugar than they took in). Even though patients continued to pass sugar in their urine until they died, despite the elimination of sugar from their diet, medical policy required that they be restrained to keep them from eating sugar. That prescientific medical belief, that eating sugar causes diabetes, is still held by a very large number, probably the majority, of physicians.

Originally, diabetes was understood to be a wasting disease, but as it became common for doctors to measure glucose, obese people were often found to have hyperglycemia, so the name diabetes has been extended to them, as type 2 diabetes. High blood sugar is often seen along with high blood pressure and obesity in Cushing's syndrome, with excess cortisol, and these features are also used to define the newer metabolic syndrome.

Following the old reasoning about the sugar disease, the newer kind of obese diabetes is commonly blamed on eating too much sugar. Obesity, especially a fat waist, and all its associated health problems, are said by some doctors to be the result of eating too much sugar, especially fructose. (Starch is the only common carbohydrate that contains no fructose.) Obesity is associated not only with diabetes or insulin resistance, but also with atherosclerosis and heart disease, high blood pressure, generalized inflammation, arthritis, depression, risk of dementia, and cancer.

There is general agreement about the problems commonly associated with obesity, but not about the causes or the way to prevent or cure obesity and the associated conditions.

In an earlier newsletter, I wrote about P. A. Piorry in Paris, in 1864, and Dr. William Budd in England, in 1867, who treated diabetes by adding a large amount of ordinary sugar, sucrose, to the patient's diet. Glucose was known to be the sugar appearing in the diabetics' urine,

but sucrose consists of half glucose, and half fructose. In 1874, E. Kulz in Germany reported that diabetics could assimilate fructose better than glucose. In the next decades there were several more reports on the benefits of feeding fructose, including the reduction of glucose in the urine. With the discovery of insulin in 1922, fructose therapy was practically forgotten, until the 1950s when new manufacturing techniques began to make it economical to use.

Its use in diabetic diets became so popular that it became available in health food stores, and was also used in hospitals for intravenous feeding.

However, while fructose was becoming popular, the cholesterol theory of heart disease was being promoted. This was the theory that eating foods containing saturated fat and cholesterol caused heart disease. (My newsletter, Cholesterol, longevity, intelligence, and health, discussed the development of that theory.)

A Swedish physician and researcher, Uffe Ravnskov, has reviewed the medical arguments for the theory that lipids in the blood are the cause of atherosclerosis and heart disease, and shows that there has never been evidence of causality, something which some people, such as Broda Barnes, understood from the beginning. In the 1950s, an English professor, John Yudkin, didn't accept the idea that eating saturated fat was the cause of high blood levels of triglycerides and cholesterol, but he didn't question the theory that lipids in the blood caused the circulatory disease. He argued that it was sugar, especially the fructose component of sucrose, rather than dietary fat, that caused the high blood lipids seen in the affluent countries, and consequently the diseases. He was sure it was a specific chemical effect of the fructose, because he argued that the nutrients that were removed in refining white flour and white sugar were insignificant, in the whole diet.

Following the publication of Yudkin's books, and coinciding with increasing promotion of the health benefits of unsaturated vegetable oils, many people were converted to Yudkin's version of the lipid theory of heart disease, i.e., that the "bad lipids" in the blood are the result of eating sugar. This has grown into essentially a cult, in which sugar is believed to act like an intoxicant, forcing people to eat until they become obese, and develop the "metabolic syndrome," and "diabetes," and the many problems that derive from that.

The publicity campaign against "saturated fat" as an ally of cholesterol derived its support from the commercial promotion of the polyunsaturated seed oils as food for humans. Although the early investigators of vitamin E knew that the polyunsaturated oils could cause sterility, and others later found that their use in commercial animal foods could cause brain degeneration, there were a few biologists (mostly associated with George Burr) who believed that this type of fatty acid is an essential nutrient.

George and Mildred Burr had created what they claimed to be a disease in rats caused by the absence of linoleic or linolenic acid in their food. Although well known researchers had previously published evidence that animals on a fat free diet were healthy—even healthier than on a normal diet—Burr and his wife published their contradictory claim without bothering to discuss the conflicting evidence. I haven't seen any instance in which Burr or his followers ever mentioned the conflicting evidence. Although other biologists didn't accept Burr's claims, and several researchers subsequently published contrary results, he later became famous when the seed oil industry wanted scientific-seeming reasons for selling their product as an "essential" food. The fact that eating the polyunsaturated fats could cause the blood cholesterol level to decrease slightly was advertised as a health benefit. Later, when human trials showed that more people on the "heart healthy" diet died of heart disease and cancer, more conventional means of advertising were used instead of human tests.

Burr's experimental diet consisted of purified casein (milk protein) and purified sucrose, supplemented with a vitamin concentrate and some minerals. Several of the B vitamins weren't known at the time, and the mineral mixture lacked zinc, copper, manganese, molybdenum, and selenium. More of the essential nutrients were unknown in his time than in Yudkin's, so his failure to consider the possibility of other nutritional deficiencies affecting health is more understandable.

In 1933, Burr observed that his fat-deficient rats consumed oxygen at an extremely high rate, and even then, the thought didn't occur to him that other nutritional deficiencies might have been involved in the condition he described. Ordinarily, the need for vitamins and minerals corresponds to the rate at which calories are being burned, the metabolic rate. Burr recalled that the rats on the fat free diet drank more water, and he reasoned that the absence of linoleic or linolenic acid in their

skin was allowing water vapor to escape at a high rate. He didn't explain why the saturated fats the rats were synthesizing from sugar didn't serve at least as well as a "vapor barrier"; they are more effective at waterproofing than unsaturated fats, because of their greater hydrophobicity. The condensed and cross-linked keratin protein in skin cells is the main reason for the skin's relatively low permeability. When an animal is burning calories at a higher rate, its sweat glands are more actively maintaining a normal body temperature, cooling by evaporation; the amount of water evaporated is an approximate measure of metabolic rate, and of thyroid function.

In 1936, a man in Burr's lab, William Brown, agreed to eat a similar diet for six months, to see whether the "essential fatty acid deficiency" affected humans as it did rats.

The diet was very similar to the rats', with a large part of the daily 2500 calories being provided at hourly intervals during the day by sugar syrup (flavored with citric acid and anise oil), protein from 4 quarts of special fat-free skimmed milk, a quart of which was made into cottage cheese, the juice of half an orange, and a "biscuit" made with potato starch, baking powder, mineral oil, and salt, with iron, viosterol (vitamin D), and carotene supplemented.

Brown had suffered from weekly migraine headaches since childhood, and his blood pressure was a little high when he began the diet. After six weeks on the diet, his migraines stopped, and never returned. His plasma inorganic phosphorus declined slightly during the experiment (3.43 mg/dL of plasma and 2.64 mg/dL on the diet, and after six months on a normal diet 4.2 mg/dL), and his total serum proteins increased from 6.98 g/dL to 8.06 g/dL on the experimental diet. His leucocyte count was lower on the high sugar diet, but he didn't experience colds or other sickness. On a normal diet, his systolic blood pressure varied from 140 mmHg to 150 mmHg, the diastolic, 95 mmHg to 100 mmHg. After a few months on the sugar and milk diet, his blood pressure had lowered to about 130 mmHg over 85 mmHg to 88 mmHg. Several months after he returned to a normal diet, his blood pressure rose to the previous level.

On a normal diet, his weight was 152 pounds, and his metabolic rate was from 9 % to 12 % below normal, but after six months on the diet it had increased to 2 % below normal. After three months on the sugar and milk diet, his weight leveled off at 138 pounds. After being on

the diet, when he ate 2000 calories of sugar and milk within two hours, his respiratory quotient would exceed 1.0, but on his normal diet his maximum respiratory quotient following those foods was less than 1.0.

The effect of diabetes is to keep the respiratory quotient low, since a respiratory quotient of one corresponds to the oxidation of pure carbohydrate, and extreme diabetics oxidize fat in preference to carbohydrate, and may have a quotient just a little above 0.7. The results of Brown's and Burr's experiments could be interpreted to mean that the polyunsaturated fats not only lower the metabolic rate, but especially interfere with the metabolism of sugars. In other words, they suggest that the normal diet is diabetogenic.

During the six months of the experiment, the unsaturation of Brown's serum lipids decreased. The authors reported that "There was no essential change in the serum cholesterol as a result of the change in diet." However, in November and December, two months before the experiment began, it had been 252 mg/dL in two measurements. At the beginning of the test, it was 298 mg/dL, two weeks later, 228 mg/dL, and four months later, 206 mg/dL. The total quantity of lipids in his blood didn't seem to change much, since the triglycerides increased as the cholesterol decreased.

By the time of Brown's experiment, other researchers had demonstrated that the cholesterol level was increased in hypothyroidism, and decreased as thyroid function, and oxygen consumption, increased. If Burr's team had been reading the medical literature, they would have understood the relation between Brown's increased metabolic rate and decreased cholesterol level. But they did record the facts, which is valuable.

The authors wrote that "The most interesting subjective effect of the 'fat-free' regimen was the definite disappearance of a feeling of fatigue at the end of the day's work."

A lowered metabolic rate and energy production is a common feature of aging and most degenerative diseases. From the beginning of an animal's life, sugars are the primary source of energy, and with maturation and aging there is a shift toward replacing sugar oxidation with fat oxidation. Old people are able to metabolize fat at the same rate as younger people, but their overall metabolic rate is lower, because they are unable to oxidize sugar at the same high rate as young people. Fat people have a similar selectively reduced ability to oxidize sugar.

Stress and starvation lead to a relative reliance on the fats stored in the tissues, and the mobilization of these as circulating free fatty acids contributes to a slowing of metabolism and a shift away from the use of glucose for energy. This is adaptive in the short term, since relatively little glucose is stored in the tissues (as glycogen), and the proteins making up the body would be rapidly consumed for energy, if it were not for the reduced energy demands resulting from the effects of the free fatty acids.

One of the points at which fatty acids suppress the use of glucose is at the point at which it is converted into fructose, in the process of glycolysis. When fructose is available, it can by-pass this barrier to the use of glucose, and continue to provide pyruvic acid for continuing oxidative metabolism, and if the mitochondria themselves aren't providing sufficient energy, it can leave the cell as lactate, allowing continuing glycolytic energy production. In the brain, this can sustain life in an emergency.

Many people lately have been told, as part of a campaign to explain the high incidence of fatty liver degeneration in the U.S., supposedly resulting from eating too much sugar, that fructose can be metabolized only by the liver. The liver does have the highest capacity for metabolizing fructose, but the other organs do metabolize it.

If fructose can by-pass the fatty acids' inhibition of glucose metabolism, to be oxidized when glucose can't, and if the metabolism of diabetes involves the oxidation of fatty acids instead of glucose, then we would expect there to be less than the normal amount of fructose in the serum of diabetics, although their defining trait is the presence of an increased amount of glucose. According toOsuagwu and Madumere,[1] that is the case. If a fructose deficiency exists in diabetes, then it is appropriate to supplement it in the diet.

Besides being one of the forms of sugar involved in ordinary energy production, interchangeable with glucose, fructose has some special functions, that aren't as well performed by glucose. It is the main sugar involved in reproduction, in the seminal fluid and intrauterine fluid, and in the developing fetus. After these crucial stages of life are past, glucose becomes the primary molecular source of energy, except when the system is under stress. It has been suggested[2] that the predominance of fructose rather than glucose in the embryo's environment helps to maintain ATP and the oxidative state (cellular redox potential) during

development in the low-oxygen environment. The placenta turns glucose from the mother's blood into fructose, and the fructose in the mother's blood can pass through into the fetus, and although glucose can move back from the fetus into the mother's blood, fructose is unable to move in that direction, so a high concentration is maintained in the fluids around the fetus.

The control of the redox potential is sometimes called the "redox signalling system," since it coherently affects all processes and conditions in the cell, including pH and hydrophobicity. For example, when a cell prepares to divide, the balance shifts strongly away from the oxidative condition, with increases in the ratios of NADH to NAD^+, of GSH to GSSG, and of lactate to pyruvate. These same shifts occur during most kinds of stress.

In natural stress, decreased availability of oxygen or nutrients is often the key problem, and many poisons can produce similar interference with energy production, for example cyanide or carbon monoxide, which block the use of oxygen, or ethanol, which inhibits the oxidation of sugars, fats, and amino acids.[3]

When oxygen isn't constantly removing electrons from cells (being chemically reduced by them) those electrons will react elsewhere, creating free radicals (including activated oxygen) and reduced iron, that will create inappropriate chemical reactions.[4,5]

Stresses and poisons of many different types, interfering with the normal flow of electrons to oxygen, produce large amounts of free radicals, which can spread structural and chemical damage, involving all systems of the cell. Ethyl alcohol is a common potentially toxic substance that can have this effect, causing oxidative damage by allowing an excess of electrons to accumulate in the cell, shifting the cells' balance away from the stable oxidized state.

Fructose has been known for many years to accelerate the oxidation of ethanol (by about 80%). Oxygen consumption in the presence of ethanol is increased by fructose more than by glucose.[6] Besides removing the alcohol from the body more quickly, it prevents the oxidative damage, by maintaining or restoring the cell's redox balance, the relatively oxidized state of the NADH/NAD^+, lactate/pyruvate, and GSH/GSSH systems. Although glucose has this stabilizing, pro-oxidative function in many situations, this is a general feature of fructose, sometimes allowing it to have the opposite effect of glucose on the cell's redox state. It

seems to be largely this generalized shift of the cell's redox state towards oxidation that is behind the ability of a small amount of fructose to catalyze the more rapid oxidation of a large amount of glucose.

Besides protecting against the reductive stresses, fructose can also protect against the oxidative stress of increased hydrogen peroxide.[7] Its metabolite, fructose 1,6-bisphosphate, is even more effective as an antioxidant.

Keeping the metabolic rate high has many benefits, including the rapid renewal of cells and their components, such as cholesterol and other lipids, and proteins, which are always susceptible to damage from oxidants, but the high metabolic rate also tends to keep the redox system in the proper balance, reducing the rate of oxidative damage.

Endotoxin absorbed from the intestine is one of the ubiquitous stresses that tends to cause free radical damage. Fructose, probably more than glucose, is protective against damage from endotoxin.

Many stressors cause capillary leakage, allowing albumin and other blood components to enter extracellular spaces or to be lost in the urine, and this is a feature of diabetes, obesity, and a variety of inflammatory and degenerative diseases including Alzheimer's disease.[8,9] Although the mechanism isn't understood, fructose supports capillary integrity; fructose feeding for 4 and 8 weeks caused a 56 % and 51 % reduction in capillary leakage, respectively.[10,11]

The ability of the mitochondria to oxidize pyruvic acid and glucose is characteristically lost to some degree in cancer. When this oxidation fails, the disturbed redox balance of the cell will usually lead to the cell's death, but if it can survive, this balance favors growth and cell division, rather than differentiated function. This was Otto Warburg's discovery, that was rejected by official medicine for 75 years.

Cancer researchers have become interested in this enzyme system that controls the oxidation of pyruvic acid (and thus sugar) by the mitochondria, since these enzymes are crucially defective in cancer cells (and also in diabetes). The chemical DCA, dichloroacetate, is effective against a variety of cancers, and it acts by reactivating the enzymes that oxidize pyruvic acid. Thyroid hormone, insulin, and fructose also activate these enzymes. These are the enzymes that are inactivated by excessive exposure to fatty acids, and that are involved in the progressive replacement of sugar oxidation by fat oxidation, during stress and aging, and in degenerative diseases; for example, a process that inactivates

the energy-producing pyruvate dehydrogenase in Alzheimer's disease has been identified.[12] Niacinamide, by lowering free fatty acids and regulating the redox system, supporting sugar oxidation, is useful in the whole spectrum of metabolic degenerative diseases.

A few times in the last 80 years, people (starting with Nasonov) have recognized that the hydrophobicity of a cell changes with its degree of excitation, and with its energy level. Recently, even in non-living physical-chemical systems, hydrophobicity and redox potential have been seen to vary together and to influence each other. Recent work shows how the oxidation of fatty acids contributes to the dissolution of mitochondria.[13] At first glance it might seem odd that the presence of fatty material could reduce the "fat loving" (lipophilic, equivalent to hydrophobic) property of a cell, but the fat used as fuel is in the form of fatty acids, which are soap-like, and spontaneously introduce "wetness" into the relatively water-resistant cell substance. The presence of fatty acids, impairing the last oxidative stage of respiration, increases the tendency of the mitochondrion to release its cytochrome c into the cell in a reduced form, leading to the apoptotic death of the cell. The oxidized form of the cytochrome is more hydrophobic, and stable.

Burr didn't understand that it was his rats' high sugar diet, freed of the anti-oxidative unsaturated fatty acids, that caused their extremely high metabolic rate, but since that time many experiments have made it clear that it is specifically the fructose component of sucrose that is protective against the antimetabolic fats.

Although Brown, et al., weren't focusing on the biological effects of sugar, their results are important in the history of sugar research because their work was done before the culture had been influenced by the development of the lipid theory of heart disease, and the later idea that fructose is responsible for increasing the blood lipids.

In 1963 and 1964, experiments[14] showed that the effects of glucose and fructose were radically affected by the type of fat in the diet. Although 0.6 % of calories as polyunsaturated fat prevents the appearance of the Mead acid (which is considered to indicate a deficiency of essential fats) the "high fructose" diets consistently add 10 % or more corn oil or other highly unsaturated fat to the diet. These large quantities of PUFA aren't necessary to prevent a deficiency, but they are needed to obscure the beneficial effects of fructose.

Many studies have found that sucrose is less fattening than starch or glucose, that is, that more calories can be consumed without gaining weight. During exercise, the addition of fructose to glucose increases the oxidation of carbohydrate by about 50 %.[15] In another experiment, rats were fed either sucrose or Coca-Cola and Purina chow, and were allowed to eat as much as they wanted.[16] They consumed 50 % more calories without gaining extra weight, relative to the standard diet.[17] observed rats given a 10.5 % or 35 % sucrose solution, or water, and observed that the sucrose increased their energy consumption by about 15 % without increasing weight gain.Macor, et al.[18] found that glucose caused a smaller increase in metabolic rate in obese people than in normal weight people, but that fructose increased their metabolic rate as much as it did that of the normal weight people. Tappy, et al.[19] saw a similar increase in heat production in obese people, relative to the effect of glucose.Brundin, et al.[20] compared the effects of glucose and fructose in healthy people, and saw a greater oxygen consumption with fructose, and also an increase in the temperature of the blood, and a greater increase in carbon dioxide production.

These metabolic effects have led several groups to recommend the use of fructose for treating shock, the stress of surgery, or infection.[21]

The commonly recommended alternative to sugar in the diet is starch, but many studies show that it produces all of the effects that are commonly ascribed to sucrose and fructose, for example hyperglycemia[22] and increased weight gain. The addition of fructose to glucose "can markedly reduce hyperglycemia during intraportal glucose infusion by increasing net hepatic glucose uptake even when insulin secretion is compromised".[23] "Fructose appears most effective in those normal individuals who have the poorest glucose tolerance".[24]

Lipid peroxidation is involved in the degenerative diseases, and many publications argue that fructose increases it, despite the fact that it can increase the production of uric acid, which is a major component of our endogenous antioxidant system.[25] When rats were fed for 8 weeks on a diet with 18 % fructose and 11 % saturated fatty acids, the content of polyunsatured fats in the blood decreased, as they had in the Brown, et al., experiment, and their total antioxidant status was increased.[26] When stroke-prone spontaneously hypertensive rats were given 60 % fructose, superoxide dismutase in their liver was increased, and the authors suggest that this "may constitute an early protective mechanism."[27] When

people were given a 300 calorie drink containing glucose, or fructose, or orange juice, those receiving the glucose had a large increase in oxidative and inflammatory stress (reactive oxygen species, and NF-kappaB binding), and those changes were absent in those receiving the fructose or orange juice.[28]

One of the observations in Brown, et al., was that the level of phosphate in the serum decreased during the experimental diet. Several later studies show that fructose increases the excretion of phosphate in the urine, while decreasing the level in the serum. However, a common opinion is that it's only the phosphorylation of fructose, increasing the amount in cells, that causes the decrease in the serum; that could account for the momentary drop in serum phosphate during a fructose load, but—since there is only so much phosphate that can be bound to intracellular fructose—it can't account for the chronic depression of the serum phosphate on a continuing diet of fructose or sucrose.

There are many reasons to think that a slight reduction of serum phosphate would be beneficial. It has been suggested that eating fruit is protective against prostate cancer, by lowering serum phosphate.[29] The aging suppressing gene discovered in 1997, named after the Greek life-promoting goddess Klotho, suppresses the reabsorption of phosphate by the kidney (which is also a function of the parathyroid hormone), and inhibits the formation of the activated form of vitamin D, opposing the effect of the parathyroid hormone. In the absence of the gene, serum phosphate is high, and the animal ages and dies prematurely. In humans, in recent years a very close association has been has been documented between increased phosphate levels, within the normal range, and increased risk of cardiovascular disease. Serum phosphate is increased in people with osteoporosis,[30] and various treatments that lower serum phosphate improve bone mineralization, with the retention of calcium phosphate.[31–35]

At high altitude, or when taking a carbonic anhydrase inhibitor, there is more carbon dioxide in the blood, and the serum phosphate is lower; sucrose and fructose increase the respiratory quotient and carbon dioxide production, and this is probably a factor in lowering the serum phosphate.

Fructose affects the body's ability to retain other nutrients, including magnesium, copper, calcium, and other minerals. Comparing diets with 20 % of the calories from fructose or from cornstarch,[36] concluded

"The results indicate that dietary fructose enhances mineral balance." Ordinarily, things (such as thyroid and vitamin D) which improve the retention of magnesium and other nutrients are considered good, but the fructose mythology allows researchers to conclude, after finding an increased magnesium balance, with either 4 % or 20 % of energy from fructose (compared to cornstarch, bread, and rice), "that dietary fructose adversely affects macromineral homeostasis in humans."[37]

Another study compared the effects of a diet with plain water, or water containing 13 % glucose, or sucrose, or fructose, or high fructose corn syrup on the properties of rats' bones: Bone mineral density and mineral content, and bone strength, and mineral balance. The largest differences were between animals drinking the glucose and the fructose solutions. The rats getting the glucose had reduced phosphorus in their bones, and more calcium in their urine, than the rats that got fructose. "The results suggested that glucose rather than fructose exerted more deleterious effects on mineral balance and bone."[38]

An older experiment compared two groups with an otherwise well balanced diet, lacking vitamin D, containing either 68 % starch or 68 % sucrose. A third group got the starch diet, but with added vitamin D. The rats on the vitamin D deficient starch diet had very low levels of calcium in their blood, and the calcium content of their bones was low, exactly what is expected with the vitamin D deficiency. However, the rats on the sucrose diet, also vitamin D deficient, had normal levels of calcium in their blood. The sucrose, unlike the starch, maintained calcium homeostasis. A radioactive calcium tracer showed normal uptake by the bone, and also apparently normal bone development, although their bones were lighter than those receiving vitamin D.

People have told me that when they looked for articles on fructose in PubMed they couldn't find anything except articles about its bad effects. There are two reasons for that. PubMed, like the earlier Index Medicus, represents the material in the National Library of Medicine, and is a medical, rather than a scientific, database, and there is a large amount of important research that it ignores. And because of the authoritarian and conformist nature of the medical profession, when a researcher observes something that is contrary to majority opinion, the title of the publication is unlikely to focus on that. In too many articles in medical journals, the title and conclusions positively misrepresent the data reported in the article.

When the idea of "glycemic index" was being popularized by dietitians, it was already known that starch, consisting of chains of glucose molecules, had a much higher index than fructose and sucrose. The more rapid appearance of glucose in the blood stimulates more insulin, and insulin stimulates fat synthesis, when there is more glucose than can be oxidized immediately. If starch or glucose is eaten at the same time as polyunsaturated fats, which inhibit its oxidation, it will produce more fat. Many animal experiments show this, even when they are intending to show the dangers of fructose and sucrose.

For example,[39] rats were fed diets with 68 % carbohydrate, 12 % fat (corn oil), and 20 % protein. In one group the carbohydrate was starch (cornstarch and maltodextrin, with a glucose equivalence of 10 %), and in other groups it was either 68 % sucrose, or 34 % fructose and 34 % glucose, or 34 % fructose and 34 % starch. (An interesting oddity, fasting triglycerides were highest in the fructose+starch group.)

The weight of their fat pads (epididymal, retroperitoneal, and mesenteric) was greatest in the fructose+starch group, and least in the sucrose group. The starch group's fat was intermediate in weight between those of the sucrose and the fructose+glucose groups.

At the beginning of the experimental diet, the average weight of the animals was 213.1 g. After five weeks, the animals in the fructose+glucose group gained 164 g, those in the sucrose group gained 177 g, and those in the starch group gained 199.2 g. The animals ate as much of the diet as they wanted, and those in the sucrose group ate the least.

The purpose of their study was to see whether fructose causes "glucose intolerance" and "insulin resistance." Since insulin stimulates appetite,[40–45] and fat synthesis, the reduced food consumption and reduced weight gain show that fructose was protecting against these potentially harmful effects of insulin.

Much of the current concern about the dangers of fructose is focussed on the cornstarch-derived high fructose corn syrup, HFCS. Many studies assume that its composition is nearly all fructose and glucose. However, Wahjudi, et al.[46] analyzed samples of it before and after hydrolyzing it in acid, to break down other carbohydrates present in it. They found that the carbohydrate content was several times higher than the listed values. "The underestimation of carbohydrate content in beverages may be a contributing factor in the development of obesity in children," and

it's especially interesting that so much of it is present in the form of starch-like materials.

Many people are claiming that fructose consumption has increased greatly in the last 30 or 40 years, and that this is responsible for the epidemic of obesity and diabetes. According to the USDA Economic Research Service, the 2007 calorie consumption as flour and cereal products increased 3 % from 1970, while added sugar calories decreased 1 %. Calories from meats, eggs, and nuts decreased 4 %, from dairy foods decreased 3 %, and calories from added fats increased 7 %. The percentage of calories from fruits and vegetables stayed the same. The average person consumed 603 calories per day more in 2007 than in 1970. If changes in the national diet are responsible for the increase of obesity, diabetes, and the diseases associated with them, then it would seem that the increased consumption of fat and starch is responsible, and that would be consistent with the known effects of starches and polyunsaturated fats.

In monkeys living in the wild, when their diet is mainly fruit, their cortisol is low, and it rises when they eat a diet with less sugar.[47] Sucrose consumption lowers ACTH, the main pituitary stress hormone,[48,49] and stress promotes increased sugar and fat consumption.[50] If animals' adrenal glands are removed, so that they lack the adrenal steroids, they choose to consume more sucrose.[51] Stress seems to be perceived as a need for sugar. In the absence of sucrose, satisfying this need with starch and fat is more likely to lead to obesity.

The glucocorticoid hormones inhibit the metabolism of sugar. Sugar is essential for brain development and maintenance. The effects of environmental stimulation and deprivation-stress can be detected in the thickness of the brain cortex in as little as 4 days in growing rats.[52] These effects can persist through a lifetime, and are even passed on transgenerationally. Experimental evidence shows that polyunsaturated (omega-3) fats retard fetal brain development, and that sugar promotes it. These facts argue against some of the currently popular ideas of the evolution of the human brain based on ancestral diets of fish or meat, which only matters as far as those anthropological theories are used to argue against fruits and other sugars in the present diet.

Honey has been used therapeutically for thousands of years, and recently there has been some research documenting a variety of uses, including treatment of ulcers and colitis, and other inflammatory con-

ditions. Obesity increases mediators of inflammation, including the C-reactive protein (CRP) and homocysteine. Honey, which contains free fructose and free glucose, lowers CRP and homocysteine, as well as triglycerides, glucose, and cholesterol, while it increased insulin more than sucrose did.[53] Hypoglycemia intensifies inflammatory reactions, and insulin can reduce inflammation if sugar is available. Obesity, like diabetes, seems to involve a cellular energy deficiency, resulting from the inability to metabolize sugar.

Sucrose (and sometimes honey) is increasingly being used to reduce pain in newborns, for minor things such as injections.[54–57] It's also effective in adults. It acts by influencing a variety of nerve systems, and also reduces stress. Insulin is probably involved in sugar analgesia, as it is in inflammation, since it promotes entry of endorphins into the brain.[58]

An extracellular phosphorylated fructose metabolite, diphosphoglycerate, has an essential regulatory effect in the blood; another fructose metabolite, fructose diphosphate, can reduce mast cell histamine release and protect against oxidative and hypoxic injury and endotoxic shock, and it reduces the expression of the inflammation mediators TNF-alpha, IL-6, nitric oxide synthase, and the activation of NF-κB, among other protective effects, and its therapeutic value is known, but its relation to dietary sugars hasn't been investigated.

A daily diet that includes two quarts of milk and a quart of orange juice provides enough fructose and other sugars for general resistance to stress, but larger amounts of fruit juice, honey, or other sugars can protect against increased stress, and can reverse some of the established degenerative conditions.

Refined granulated sugar is extremely pure, but it lacks all of the essential nutrients, so it should be considered as a temporary therapeutic material, or as an occasional substitute when good fruit isn't available, or when available honey is allergenic.

Suitable Fats, Unsuitable Fats

Issues in Nutrition

Ray Peat's Newsletter, 2007

For fifty years, the mass media have been making the public think about the fats in their diet, filling the culture with clichés about bad saturated animal fats that raise cholesterol, or lately the trans-fats in margarine, and images of arteries clogged by bad fats. The public instruction about the fats we should eat resembles the owner's manual for a car, that tells you what kind of motor oil and fuel and coolant to use; they are telling us that they know how our body works, and that they know what it needs. But now, even after the human genome has supposedly been partly "decoded," the biological functions of the fats have hardly begun to be investigated.

To understand the present issues regarding fats in nutrition and medicine it's helpful to look at the historical development of biochemical and physiological fat research in a variety of contexts, including agriculture and economics, as well as considering the effects of the changing ideas about cell structure, vitamins, hormones, immunology, brain development, evolution, and the growing understanding of the way physiology interacts with ecology. We need to recognize the complexity of the physiology of fats, to appreciate the complexity of the living organism.

Financial considerations have driven fat research in very obvious ways. In 1883, Mark Twain described how commercial fraud was making use of new technology to substitute cheap fats and oils for butter and olive oil. Hard fats such as tallow, which had been used for making soap and candles, began to be widely used as a substitute for butter in the 19th century. Around 1912, chemists found economical ways to solidify (for use as a butter substitute) the very cheap liquid oils, such as cottonseed oil, linseed oil, whale oil, and fish oils, which been used mostly as fuels or varnish. The seed oils were so cheap that meat packers quickly became major producers of hydrogenated cottonseed and soy oils, to extend their limited supply of lard or tallow for sale as shortening or margarine.

Between 1912 and 1927 there were several studies that reported that animals could live on a fat-free diet, and that in fact they lived longer,

and without the normal mortality from cancer. In the 1940s and 1950s, most textbooks that mentioned the idea that certain fats were essential nutrients described it as a controversial idea. But the oil industries used public relations effectively to sell the medical (heart protective) benefits of a diet containing increased amounts of linoleic and linolenic acids, which they called the essential fatty acids. They began citing a 1929 publication[1] that claimed to demonstrate the essentiality of those fatty acids, while ignoring the publications that pointed in different directions.

The cheapness of the seed oils led to their use in animal feeds, to promote growth. By the 1940s, the polyunsaturated oils, including fish oils, were known to cause deterioration of the brain, muscles, and gonads in a variety of animals, and this was found to be caused mainly by their destruction of vitamin E. A little later, the disease called steatitis or yellow fat disease was found to be produced in various animals that were fed too much fish or fish oil.

The reason linseed oil and fish oil were used for making varnishes and paints was that they are "drying oils," reacting with oxygen to polymerize and harden. The physical and chemical properties of the oils are fairly well understood, and among the polyunsaturated fatty acids (PUFA) the omega-3 fatty acids react most easily with oxygen. Heat, light, and moisture increase their spontaneous interactions with oxygen, and besides polymerizing, these oils produce a variety of reactive particles, including acrolein, which combine with other substances, such as cellular proteins and DNA, with highly toxic effects. At low temperatures and low oxygen concentrations these oils are not highly reactive. Fats that harden at low temperatures (as saturated fats do) wouldn't be convenient for organisms that live in a cool environment, and so organisms regulate the type of fat they synthesize according to the temperature of their tissues. The fact that certain types of polyunsaturated fatty acids function nicely in fish, worms, and insects, doesn't mean that they are ideal fats for mammals.

The fact that vitamin E prevented or cured some of the major diseases in farm animals caused by excessive PUFA, and that it could retard the development of rancidity in stored oils, led quickly to the persistent belief that lipid peroxidation is the only toxic effect of the vegetable oils. However, the oils were being seen to cause other problems, including accelerated aging and obesity, but those problems weren't of interest to farmers, who wanted to sell plump young animals as cheaply and

quickly as possible. Even fresh oils have toxic effects, and the oxidative damage they do is often the consequence of these other toxic actions.

Another cheap food additive, coconut oil, was found to increase feed consumption while slowing weight gain, so it wasn't popular in the meat industry. The highly unsaturated seed oils had the opposite effect, of producing a rapid fattening of the animal, while decreasing feed consumption, so by 1950 corn and soybeans were widely considered to be optimal feeds for maximizing profits in the production of meat animals. It was at this time that the industry found that it could market the liquid oils directly to consumers, as health-promoting foods, without bothering to turn them into solid shortening or margarine. Somehow, few physiologists continued to think about the implications of metabolic slowing, obesity, and the related degenerative diseases.

As vitamin research advanced in the 1940s, Roger Williams' lab at the Clayton Foundation Biochemical Institute, University of Texas at Austin, recognized the "fat deficiency disease" of the Burrs as a deficiency of vitamin B_6, and showed that when they produced the condition with a diet similar to the one the Burrs had used, they could cure it by administering vitamin B_6. In the early 1930s George Burr had discovered that animals on a fat free diet had an extremely high rate of metabolism, but he didn't investigate the important ramifications of that observation, such as their increased need for vitamins and minerals, in accordance with their rate of metabolism. The PUFA slowed metabolism, and that effect was good for agriculture.

The commercial pressure on fat research has created a new way of writing research reports, that several decades earlier wouldn't have been acceptable. For example, the effects of a specific fat on a few of the components of a complex process such as clotting are often described in the title, introduction, and conclusion of an article as if they were revealing a way to prevent heart disease. The effects of unsaturated fats on cells *in vitro* are often the opposite of their effects in living animals, but editors are allowing authors to claim that their *in vitro* results justify dietary or therapeutic use of the fats. Journals of medicine and nutrition are now preferred sites for commercial press releases, composed to superficially resemble scientific reports.

The suppressive effects of unsaturated fats on mitochondrial energy production have been widely investigated, since it is that effect that makes animal fattening with PUFA so economical. Rather than inter-

preting that as a toxic effect, using the innate structure and function of the mitochondrion as a point of reference from which to evaluate dietary components, the consumption of "good" oils is being used as the reference point from which to evaluate the meaning of metabolism ("efficiency is good," "low oxygen consumption is good"). Building on the idea that the oils are health-promoters which increase metabolic efficiency, the never-viable "rate of aging" theory was resuscitated: The anti-respiratory effect of PUFA is used (illogically) to return to the idea that aging occurs in proportion to the amount of oxygen consumed, because animals which lack the supposedly essential nutrients ("defective animals") consume oxygen rapidly—burning calories rapidly, they are supposed to be like a candle that won't last as long if it burns intensely. The old theory is simply resuscitated to explain why the anti-respiratory action of PUFA might be beneficial, justifying further promotion of their use as food and drugs.

Ordinarily, in biochemistry and physiology the inhibition of an enzyme is taken as a suggestion of toxicity, but when the point of reference is the idea of the goodness of PUFA, the activity of an intrinsic enzyme is taken to be evidence of harm, and its inhibition (by PUFA) is taken to be the proper, healthful situation. The enzyme that produces the Mead fatty acid is strongly inhibited by PUFA seed oils (less strongly by fish oils), and so the presence of the Mead acid in the tissues is taken as evidence that the animal is suffering damage resulting from the absence of PUFA. The Mead acid happens to have some valuable anti-inflammatory effects, and is associated with many biological advantages, but research in that direction is prevented by the lack of funding.

By 1920, the polyunsaturated fatty acids were recognized to inhibit proteolytic enzymes. At that time, the production of unsaturated fat was considered to be a feature of certain pathogens, able to overcome the proteolytic-phagocytic functions of the immune system.

Scattered studies have found that polyunsaturated fats inhibit the proteolytic enzymes involved in the digestion of food, in the removal of clots, in the formation of thyroid hormone, and many other essential physiological processes. But currently, the only implication being drawn from this broad class of effects of the PUFA is that some proteolytic enzymes are involved in disease processes, and consequently increased consumption of PUFA would be appropriate, because of their ability to suppress a conditionally harmful proteolytic enzyme. Since the organ-

ism consists mainly of proteins, there are complex innate systems for regulating the proteolytic enzymes, activating or inactivating them as needed, and such complexity isn't likely to depend on variable, unstable dietary factors. Exogenous substances that inhibit some proteases could create an unlimited variety of functional and anatomical irregularities.

Some of the interesting enzymes affected specifically by polyunsaturated fatty acids are those involved in hormone production. While they inhibit the formation of progesterone and androgens, they activate the synthesis of estrogen, which in turn activates the release of more free polyunsaturated fatty acids from the tissues, in a positive feedback pattern.

The inhibition of detoxification enzymes by PUFA[2] affects many processes, such as the elimination of estrogen, contributing to the positive feedback between estrogen and the oils. The meaning of this tends to be lost, because of the estrogen industry's effective campaigns.

Another situation in which fatty acids participate in a positive feedback system is the stress reaction, in which the released fatty acids impair mitochondrial energy production, increasing the stress and leading to further release of fatty acids.

One of the perennial theories of aging that has remained viable is the metaplasm/lipofuscin/age pigment theory, the idea that a toxic material accumulates in tissues over time. The age pigment contains proteins, cross-linked PUFA, and metals. The inhibition of proteolytic enzymes is involved in its accumulation, and the ratio of PUFA to saturated fatty acids is an important factor in its formation. Estrogen is one of the factors that can promote the formation of age pigment, probably partly because its lipolytic action increases the cells' exposure to free fatty acids. The lipofuscin contributes to inhibition of proteolysis, probably partly through increased production of free radicals and hydrogen peroxide.

The proteolytic enzymes are an essential part of innate immunity, and the highly unsaturated fatty acid, EPA, which is the most immunosuppressive of the fats, strongly inhibits proteolysis in some cells. The natural killer (NK) cells and phagocytic cells are two types of cell that are suppressed by PUFA, and they are involved in many kinds of physiological events, not just the killing of tumor cells and virus infected cells.

The immunosuppressive effects of PUFA are very general. Many metabolites that are known to have harmful effects on the immune

system are increased by the PUFA (histamine,[3] serotonin, lactate, nitric oxide[4]). These substances are also involved in tumor development.

Besides inhibiting enzymes and being converted into prostaglandins, the polyunsaturated fatty acids have direct effects, as signals (or interference with signals) on many tissues. The belief that the PUFA are essential nutrients has influenced the way cellular excitability thresholds are being interpreted. Anxiety and panic may be interpreted as alertness, calmness may be interpreted as stupidity. Specifically, long-term potentiation (LTP) may contribute to seizures, senility, and excitotoxicity, as well as to learning, but many titles and conclusions equate increased LTP with "improved LTP," implying that it has biological value to the animal.

The ability of nerve cells to become quiescent after excitation is essential to learning and perception. This ability is lost with aging, as the functional balance in the brain shifts away from GABA-ergic to glutamatergic nerves. The polyunsaturated fatty acids promote the excitatory nervous state. The combination of respiratory inhibition with excitation can produce excitotoxic cell death. If the doctrine of "essentiality of PUFA" hadn't been so influential, different interpretations of excitatory thresholds, energy metabolism, and even cell structure would have been allowed to develop more fully.

The concentration of polyunsaturated fats in the brain has led many people to say that the "nutritionally essential fatty acids," especially the omega-3 fatty acids, are essential for brain development (for the formation of nerve cell membranes), and for the formation of synapses, and that increasing the amount of those fats in the diet would be desirable. The types of argument they use simply ignore the real evidence: Cells can multiply indefinitely in culture dishes without the essential fatty acids, insects can multiply for generations on diets without the unsaturated fats, forming normal synapses and brains, and mammals fed diets with extremely small amounts of the unsaturated fats grow with perfectly normal—possibly superior—brains.

One of the fats in the omega-9 series, that the human body can synthesize, nervonic acid, is a major constituent of brain tissue, but its important functions in brain development have hardly been investigated. Unlike the unsaturated fatty acids oleic acid, linoleic acid, and eicosapentaenoic acid (EPA), nervonic acid isn't associated with the "coronary risk factors," and it has been suggested that it might be used in adults to prevent obesity-related diseases.[5]

One major area of research that has been neglected involves the role of fats in modifying the ways in which proteins and nucleic acids interact with water—arguably the most basic of all physiological processes. Unsaturated fats are more water soluble than saturated fats, and they are involved in many problems of permeability and edema.

In aging and evolution, there are systematic changes in tissue water content that appear to correspond to changes in rate of metabolism, to the degree of unsaturation of cellular fats, and to thyroid function and temperature. Metabolic intensity and longevity can be modified by changing the degree of saturation of fats in the diet and tissues, but—despite almost a century of sporadic investigations—no one has yet worked out in detail the most appropriate way to do this. But it has become clear that the "uncoupled" mitochondrion, that "wastes oxygen and calories," is protective against free radicals, cancer, and aging. Thyroid hormone and the absence of PUFA are important factors in supporting the "wasteful" mitochondrion.

Although the complex interactions of anatomy, energy, temperature, fat nutrition, tissue water content, and hormones haven't been systematically investigated, some of the principles regarding the biological suitability of specific fats are already being applied in the limited context of therapy.

At present, the most important issue is to recognize the dangers presented by the intrusion of corporate power into science, especially as it relates to nutrition and medicine, and to consider the implications of the known effects of the PUFA on all of our biological systems.

The food-derived polyunsaturated fatty acids play important roles in the development of all of the problems associated with aging—reduced immunity, insomnia, decreased learning ability, substitution of fat for muscle, susceptibility to tissue peroxidation and inflammation, growth of tumors, etc., and are probably involved in most other health problems, even in children. If research hadn't been guided by the economic interests of the seed oil industry, many of those problems would have been solved by now.

The influence of the mass media on science can be seen in two issues that are currently well known.

A popular test used for evaluating diabetes is the measurement of glycated hemoglobin, the attachment of a sugar-like fragment to the protein of hemoglobin. This is used to judge whether blood sugar is

being controlled adequately. The glycation of proteins is widely believed to be a central process in aging, and is often used to argue that people should reduce their sugar consumption.

Another well publicized problem supposedly involving the reaction between sugars and proteins has to do with the discovery of the carcinogen, acrylamide, in breads and french fries. The Whole Foods Market was sued in California for selling whole wheat bread without a warning that it contained a carcinogen.

But the changes in proteins that occur in diabetes are mainly produced by the breakdown products of polyunsaturated fatty acids. Acrylamide is produced largely by the reaction of PUFA with proteins.

Sugar, by reducing the level of free fatty acids in the body, actually tends to protect against these toxic effects of the PUFA. Diabetes, like cancer, has been known for a long time to be promoted by unsaturated oils in the diet, rather than by sugar. The seed oil industry has been more effective than the sugar industry in lobbying and advertising, and the effects can be seen in the assumptions that shape medical and biological research.

TSH, Temperature, Pulse Rate, and Other Indicators in Hypothyroidism

Ray Peat's Newsletter, 2007

- Each of the indicators of thyroid function can be useful, but has to be interpreted in relation to the physiological state.
- Increasingly, TSH (the pituitary thyroid stimulating hormone) has been treated as if it meant something independently; however, it can be brought down into the normal range, or lower, by substances other than the thyroid hormones.
- "Basal" body temperature is influenced by many things besides thyroid. The resting heart rate helps to interpret the temperature. In a cool environment, the temperature of the extremities is sometimes a better indicator than the oral or eardrum temperature.
- The "basal" metabolic rate, especially if the rate of carbon dioxide production is measured, is very useful. The amount of water and calories disposed of in a day can give a rough idea of the metabolic rate.
- The T wave on the electrocardiogram, and the relaxation rate on the Achilles reflex test are useful.
- Blood tests for cholesterol, albumin, glucose, sodium, lactate, total thyroxine and total T_3 are useful to know, because they help to evaluate the present thyroid status, and sometimes they can suggest ways to correct the problem.
- Less common blood or urine tests (adrenaline, cortisol, ammonium, free fatty acids), if they are available, can help to understand compensatory reactions to hypothyroidism.
- A book such as McGavack's *The Thyroid*, that provides traditional medical knowledge about thyroid physiology, can help to dispel some of the current dogmas about the thyroid.
- Using more physiologically relevant methods to diagnose hypothyroidism will contribute to understanding its role in many problems now considered to be unrelated to the thyroid.

I have spoken to several people who told me that their doctors had diagnosed them as "both hypothyroid and hyperthyroid." Although physicists can believe in things which are simultaneously both particles

and not particles, I think biology (and medicine, as far as it is biologically based) should occupy a world in which things are not simultaneously themselves and their opposites. Those illogical, impossible diagnoses make it clear that the rules for interpreting test results have in some situations lost touch with reality.

Until the 1940s, hypothyroidism was diagnosed on the basis of signs and symptoms, and sometimes the measurement of oxygen consumption ("basal metabolic rate") was used for confirmation. Besides the introduction of supposedly "scientific" blood tests, such as the measurement of protein-bound iodine (PBI) in the blood, there were other motives for becoming parsimonious with the diagnosis of hypothyroidism. With the introduction of synthetic thyroxine, one of the arguments for increasing its sale was that natural Armour thyroid (which was precisely standardized by biological tests) wasn't properly standardized, and that an overdose could be fatal. A few articles in prestigious journals created a myth of the danger of thyroid, and the synthetic thyroxine was (falsely) said to be precisely standardized, and to be without the dangers of the complete glandular extract.

Between 1940 and about 1950, the estimated percentage of hypothyroid Americans went from 30 % or 40 % to 5 %, on the basis of the PBI test, and it has stayed close to that lower number (many publications claim it to be only 1 % to 2 %). By the time that the measurement of PBI was shown to be only vaguely related to thyroid hormonal function, it had been in use long enough for a new generation of physicians to be taught to disregard the older ideas about diagnosing and treating hypothyroidism. They were taught to inform their patients that the traditional symptoms that were identified as hypothyroidism before 1950 were the result of the patients' own behavior (sloth and gluttony, for example, which produced fatigue, obesity, and heart disease), or that the problems were imaginary (women's hormonal and neurological problems, especially), or that they were simply mysterious diseases and defects (recurring infections, arthritis, and cancer, for example).

As the newer, more direct tests became available, their meaning was defined in terms of the statistical expectation of hypothyroidism that had become an integral part of medical culture. To make the new TSH measurements fit the medical doctrine, an 8- or 10-fold variation in the hormone was defined as "normal." With any other biological measurement, such as erythrocyte count, blood pressure, body weight,

or serum sodium, calcium, chloride, or glucose, a variation of 10 % to 20 % from the mean is considered to be meaningful. If the doctrine regarding the 5 % prevalence of hypothyroidism hadn't been so firmly established, there would have been more interest in establishing the meaning of these great variations in TSH.

In recent years the "normal range" for TSH has been decreasing. In 2003, the American Association of Clinical Endocrinologists changed their guidelines for the normal range to 0.3 μIU/mL to 3.0 μIU/mL. But even though this lower range is less arbitrary than the older standards, it still isn't based on an understanding of the physiological meaning of TSH.

Over a period of several years, I never saw a person whose TSH was over 2 μIU/mL who was comfortably healthy, and I formed the impression that the normal, or healthy, quantity was probably something less than 1.0.

If a pathologically high TSH is defined as normal, its role in major diseases, such as breast cancer, mastalgia, MS, fibrotic diseases, and epilepsy, will simply be ignored. Even if the possibility is considered, the use of an irrational norm, instead of a proper comparison, such as the statistical difference between the mean TSH levels of cases and controls, leads to denial of an association between hypothyroidism and important diseases, despite evidence that indicates an association.

Some critics have said that most physicians are "treating the TSH," rather than the patient. If TSH is itself pathogenic, because of its pro-inflammatory actions, then that approach isn't entirely useless, even when they "treat the TSH" with only thyroxine, which often isn't well converted into the active triiodothyronine, T_3. But the relief of a few symptoms in a small percentage of the population is serving to blind the medical world to the real possibilities of thyroid therapy.

TSH has direct actions on many cell types other than the thyroid, and probably contributes directly to edema,[1] fibrosis, and mastocytosis. If people are concerned about the effects of a TSH "deficiency," then I think they have to explain the remarkable longevity of the animals lacking pituitaries in W.D. Denckla's experiments, or of the naturally pituitary deficient dwarf mice that lack TSH, prolactin, and growth hormone, but live about a year longer than normal mice.[2] Until there is evidence that very low TSH is somehow harmful, there is no basis for setting a lower limit to the normal range.

Some types of thyroid cancer can usually be controlled by keeping TSH completely suppressed. Since TSH produces reactions in cells as different as fibroblasts and fat cells, pigment cells in the skin, mast cells and bone marrow cells,[3] it won't be surprising if it turns out to have a role in the development of a variety of cancers, including melanoma.

Many things, including the liver and the senses, regulate the function of the thyroid system, and the pituitary is just one of the factors affecting the synthesis and secretion of the thyroid hormones.

A few people who had extremely low levels of pituitary hormones, and were told that they must take several hormone supplements for the rest of their life, began producing normal amounts of those hormones within a few days of eating more protein and fruit. Their endocrinologist described them as, effectively, having no pituitary gland. Extreme malnutrition in Africa has been described as creating "…a condition resembling hypophysectomy,"[4] but the people I talked to in Oregon were just following what they thought were healthful nutritional policies, avoiding eggs and sugars, and eating soy products.

Occasionally, a small supplement of thyroid in addition to a good diet is needed to quickly escape from the stress-induced "hypophysectomized" condition.

Aging, infection, trauma, prolonged cortisol excess, somatostatin, dopamine or L-dopa, adrenaline,[5] amphetamine, caffeine and fever can lower TSH, apart from the effect of feedback by the thyroid hormones, creating a situation in which TSH can appear normal or low, at the same time that there is a real hypothyroidism.

A disease or its treatment can obscure the presence of hypothyroidism. Parkinson's disease is a clear example of this. (Garcia-Moreno and Chacon, 2002: "…in the same way hypothyroidism can simulate Parkinson's disease, the latter can also conceal hypothyroidism.")

The stress-induced suppression of TSH and other pituitary hormones is reminiscent of the protective inhibition that occurs in individual nerve fibers during dangerously intense stress, and might involve such a "parabiotic" process in the nerves of the hypothalamus or other brain region. The relative disappearance of the pituitary hormones when the organism is in very good condition (for example, the suppression of ACTH and cortisol by sugar or pregnenolone) is parallel to the high energy quiescence of individual nerve fibers.

These associations between energy state and cellular activity can be used for evaluating the thyroid state, as in measuring nerve and muscle reaction times and relaxation rates. For example, relaxation which is retarded, because of slow restoration of the energy needed for cellular "repolarization," is the basis for the traditional use of the Achilles tendon reflex relaxation test for diagnosing hypothyroidism. The speed of relaxation of the heart muscle also indicates thyroid status.[6]

Stress, besides suppressing the TSH, acts in other ways to suppress the real thyroid function. Cortisol, for example, inhibits the conversion of T_4 to T_3, which is responsible for the respiratory production of energy and carbon dioxide. Adrenaline, besides leading to increased production of cortisol, is lipolytic, releasing the fatty acids which, if they are polyunsaturated, inhibit the production and transport of thyroid hormone, and also interfere directly with the respiratory functions of the mitochondria. Adrenaline decreases the conversion to T_4 to T_3, and increases the formation of the antagonistic reverse T_3.[7,8]

During the night, at the time adrenaline and free fatty acids are at their highest, TSH usually reaches its peak. TSH itself can produce lipolysis, raising the level of circulating free fatty acids. This suggests that a high level of TSH could sometimes contribute to functional hypothyroidism, because of the antimetabolic effects of the unsaturated fatty acids.

These are the basic reasons for thinking that the TSH tests should be given only moderate weight in interpreting thyroid function.

The metabolic rate is very closely related to thyroid hormone function, but defining it and measuring it have to be done with awareness of its complexity.

The basal metabolic rate that was commonly used in the 1930s for diagnosing thyroid disorders was usually a measurement of the rate of oxygen consumption, made while lying quietly early in the morning without having eaten anything for several hours. When carbon dioxide production can be measured at the same time as oxygen consumption, it's possible to estimate the proportion of energy that is being derived from glucose, rather than fat or protein, since oxidation of glucose produces more carbon dioxide than oxidation of fat does. Glucose oxidation is efficient, and suggests a state of low stress.

The very high adrenaline that sometimes occurs in hypothyroidism will increase the metabolic rate in several ways, but it tends to increase

the oxidation of fat. If the production of carbon dioxide is measured, the adrenaline/stress component of metabolism will be minimized in the measurement. When polyunsaturated fats are mobilized, their spontaneous peroxidation consumes some oxygen, without producing any usable energy or carbon dioxide, so this is another reason that the production of carbon dioxide is a very good indicator of thyroid hormone activity. The measurement of oxygen consumption was usually done for two minutes, and carbon dioxide production could be accurately measured in a similarly short time. Even a measurement of the percentage of carbon dioxide at the end of a single breath can give an indication of the stress-free, thyroid hormone stimulated rate of metabolism (it should approach five or six percent of the expired air).

Increasingly in the last several years, people who have many of the standard symptoms of hypothyroidism have told me that they are hyperthyroid, and that they have to decide whether to have surgery or radiation to destroy their thyroid gland. They have told me that their symptoms of "hyperthyroidism," according to their physicians, were fatigue, weakness, irritability, poor memory, and insomnia.

They didn't eat very much. They didn't sweat noticeably, and they drank a moderate amount of fluids. Their pulse rates and body temperature were normal, or a little low.

Simply on the basis of some laboratory tests, they were going to have their thyroid gland destroyed. But on the basis of all of the traditional ways of judging thyroid function, they were hypothyroid.

Broda Barnes, who worked mostly in Fort Collins, Colorado, argued that the body temperature, measured before getting out of bed in the morning, was the best basis for diagnosing thyroid function.

Fort Collins, at a high altitude, has a cool climate most of the year. The altitude itself helps the thyroid to function normally. For example, one study[9] showed an 18 % increase in T_3 at a high altitude, and mitochondria become more numerous and are more efficient at preventing lactic acid production, capillary leakiness, etc.

In Eugene during a hot and humid summer, I saw several obviously hypothyroid people whose temperature seemed perfectly normal, euthyroid by Barnes' standards. But I noticed that their pulse rates were, in several cases, very low. It takes very little metabolic energy to keep the body at 98.6 °F when the air temperature is in the nineties. In cooler

weather, I began asking people whether they used electric blankets, and ignored their temperature measurements if they did.

The combination of pulse rate and temperature is much better than either one alone. I happened to see two people whose resting pulse rates were chronically extremely high, despite their hypothyroid symptoms. When they took a thyroid supplement, their pulse rates came down to normal. (Healthy and intelligent groups of people have been found to have an average resting pulse rate of 85/minute, while less healthy groups average close to 70/minute.)

The speed of the pulse is partly determined by adrenaline, and many hypothyroid people compensate with very high adrenaline production. Knowing that hypothyroid people are susceptible to hypoglycemia, and that hypoglycemia increases adrenaline, I found that many people had normal (and sometimes faster than average) pulse rates when they woke up in the morning, and when they got hungry. Salt, which helps to maintain blood sugar, also tends to lower adrenalin, and hypothyroid people often lose salt too easily in their urine and sweat. Measuring the pulse rate before and after breakfast, and in the afternoon, can give a good impression of the variations in adrenalin. (The blood pressure, too, will show the effects of adrenaline in hypothyroid people. Hypothyroidism is a major cause of hypertension.)

But hypoglycemia also tends to decrease the conversion of T_4 to T_3, so heat production often decreases when a person is hungry. First, their fingers, toes, and nose will get cold, because adrenalin, or adrenergic sympathetic nervous activity, will increase to keep the brain and heart at a normal temperature, by reducing circulation to the skin and extremities. Despite the temperature-regulating effect of adrenalin, the reduced heat production resulting from decreased T_3 will make a person susceptible to hypothermia if the environment is cool.

Since food, especially carbohydrate and protein, will increase blood sugar and T_3 production, eating is "thermogenic," and the oral (or eardrum) temperature is likely to rise after eating.

Blood sugar falls at night, and the body relies on the glucose stored in the liver as glycogen for energy, and hypothyroid people store very little sugar. As a result, adrenalin and cortisol begin to rise almost as soon as a person goes to bed, and in hypothyroid people, they rise very high, with the adrenalin usually peaking around 1 or 2 A.M., and the cortisol peaking around dawn; the high cortisol raises blood sugar as

morning approaches, and allows adrenalin to decline. Some people wake up during the adrenalin peak with a pounding heart, and have trouble getting back to sleep unless they eat something.

If the night-time stress is very high, the adrenalin will still be high until breakfast, increasing both temperature and pulse rate. The cortisol stimulates the breakdown of muscle tissue and its conversion to energy, so it is thermogenic, for some of the same reasons that food is thermogenic.

After eating breakfast, the cortisol (and adrenalin, if it stayed high despite the increased cortisol) will start returning to a more normal, lower level, as the blood sugar is sustained by food, instead of by the stress hormones. In some hypothyroid people, this is a good time to measure the temperature and pulse rate. In a normal person, both temperature and pulse rate rise after breakfast, but in very hypothyroid people either, or both, might fall.

Some hypothyroid people have a very slow pulse, apparently because they aren't compensating with a large production of adrenalin. When they eat, the liver's increased production of T_3 is likely to increase both their temperature and their pulse rate.

By watching the temperature and pulse rate at different times of day, especially before and after meals, it's possible to separate some of the effects of stress from the thyroid-dependent, relatively "basal" metabolic rate. When beginning to take a thyroid supplement, it's important to keep a chart of these measurements for at least two weeks, since that's roughly the half-life of thyroxine in the body. When the body has accumulated a steady level of the hormones, and begun to function more fully, the factors such as adrenaline that have been chronically distorted to compensate for hypothyroidism will have begun to normalize, and the early effects of the supplementary thyroid will in many cases seem to disappear, with heart rate and temperature declining. The daily dose of thyroid often has to be increased several times, as the state of stress and the adrenaline and cortisol production decrease.

Counting calories achieves approximately the same thing as measuring oxygen consumption, and is something that will allow people to evaluate the various thyroid tests they may be given by their doctor. Although food intake and metabolic rate vary from day to day, an approximate calorie count for several days can often make it clear that a diagnosis of hyperthyroidism is mistaken. If a person is eating only

about 1800 calories per day, and has a steady and normal body weight, any "hyperthyroidism" is strictly metaphysical, or as they say, "clinical."

When the humidity and temperature are normal, a person evaporates about a liter of water for every 1000 calories metabolized. Eating 2000 calories per day, a normal person will take in about four liters of liquid, and form about two liters of urine. A hyperthyroid person will invisibly lose several quarts of water in a day, and a hypothyroid person may evaporate a quart or less.

When cells, because of a low metabolic rate, don't easily return to their thoroughly energized state after they have been stimulated, they tend to take up water, or, in the case of blood vessels, to become excessively permeable. Fatigued muscles swell noticeably, and chronically fatigued nerves can swell enough to cause them to be compressed by the surrounding connective tissues. The energy and hydration state of cells can be detected in various ways, including magnetic resonance, and electrical impedance, but functional tests are easy and practical.

With suitable measuring instruments, the effects of hypothyroidism can be seen as slowed conduction along nerves, and slowed recovery and readiness for new responses. Slow reaction time is associated with slowed memory, perception, and other mental processes. Some of these nervous deficits can be remedied slightly just by raising the core temperature and providing suitable nutrients, but the active thyroid hormone, T_3 is mainly responsible for maintaining the temperature, the nutrients, and the intracellular respiratory energy production.

In nerves, as in other cells, the ability to rest and repair themselves increases with the proper level of thyroid hormone. In some cells, the energized stability produced by the thyroid hormones prevents inflammation or an immunological hyperactivity. In the 1950s, shortly after it was identified as a distinct substance, T_3 was found to be anti-inflammatory, and both T_4 and T_3 have a variety of anti-inflammatory actions, besides the suppression of the pro-inflammatory TSH.

Because the actions of T_3 can be inhibited by many factors, including polyunsaturated fatty acids, reverse T_3, and excess thyroxine, the absolute level of T_3 can't be used by itself for diagnosis. "Free T_3" or "free T_4" is a laboratory concept, and the biological activity of T_3 doesn't necessarily correspond to its "freedom" in the test. T_3 bound to its transport proteins can be demonstrated to enter cells, mitochondria, and nuclei. Transthyretin, which carries both vitamin A and thyroid hormones, is

sharply decreased by stress, and should probably be regularly measured as part of the thyroid examination.

When T_3 is metabolically active, lactic acid won't be produced unnecessarily, so the measurement of lactate in the blood is a useful test for interpreting thyroid function. Cholesterol is used rapidly under the influence of T_3, and ever since the 1930s it has been clear that serum cholesterol rises in hypothyroidism, and is very useful diagnostically. Sodium, magnesium, calcium, potassium, creatinine, albumin, glucose, and other components of the serum are regulated by the thyroid hormones, and can be used along with the various functional tests for evaluating thyroid function.

Stereotypes are important. When a very thin person with high blood pressure visits a doctor, hypothyroidism isn't likely to be considered; even high TSH and very low T_4 and T_3 are likely to be ignored, because of the stereotypes. (And if those tests were in the healthy range, the person would be at risk for the "hyperthyroid" diagnosis.) But remembering some of the common adaptive reactions to a thyroid deficiency, the catabolic effects of high cortisol and the circulatory disturbance caused by high adrenaline should lead to doing some of the appropriate tests, instead of treating the person's hypertension and "under nourished" condition.

The Cancer Matrix

Ray Peat's Newsletter, 2015

The U.S. government (NIH, CDC) provides a cancer curriculum to schools. For high school, grades 9-12, they explain that a series of gene mutations causes it. In grade school, the basic idea of the cancer curriculum is just to teach them to fear cancer and the sunlight which, according to the curriculum, seems to be a very important mutagen.

The gene mutation theory of cancer is sustained by a broader mystique of "genetics" in our culture. Over 100 years ago, an ideology of chance and random changes in organisms was superimposed onto the theory of evolution. After 1944, when Avery, MacLeod and McCarty showed that strands of DNA carry hereditary information, the doctrine of random change took on a specific chemical meaning—changes in the sequence of bases in the DNA molecule. This made it easier to disregard the evidence of the inheritance of acquired changes, since chemical, even biochemical, reactions are usually interpreted statistically, with an assumption of randomness. If the changes in the DNA code are random, and not influenced by the organism's physiology and biochemistry, then the four nucleotides that make up DNA (abbreviated G, C, A, and T) should show a random composition, but in fact the ratio of GC pairs to AT pairs varies in different types of organism, and in mitochondrial DNA, the GC (guanine-cytosine) content corresponds closely to the rate of oxidative metabolism and longevity.[1]

The official (government and American Cancer Society) view of cancer is that a tumor consists of the descendants of a single mutated cell. A current "proof" of this is that in a given tumor, all of the X chromosomes which are active have the same genetic composition, while in the rest of the organism, the X chromosome which remains active is a matter of chance. That shows, they argue, that the tumor must have developed from a cell in which that chromosome was active, not from a group of cells. However, non-random inactivation of X chromosomes is now known to occur, and that it involves epigenetic imprinting processes, such as methylation.[2,3] Mary Lyon, the person who discovered that females inactivate one of their X chromosomes, has recognized the complexity of the process.[4] In arguing against the idea that the

development of cancer is an epigenetic process, the cancer-gene people have invoked a process that responds to epigenetic influences.

The assumption of randomness, and the assertions of the cancer doctors who subscribe to the doctrine, have had terrible effects on biology and medicine. Following the doctrine, their treatments must concentrate on eliminating every single cell of the cancer clone. Since surgery can't eliminate defective cells that have entered the blood stream, radiation and chemical toxins are logical necessities. Since mutations are random events, the person's general health is of little importance to the oncologist. Typically, they will tell the patient that their diet doesn't matter, except that they should avoid antioxidants if they are going to have radiation therapy.

For centuries, the definition of a malignant tumor has been that it's one which will return after it has been cut out. In recent years, the definition has been extended to those that return after the original tumor has been eliminated by radiation or chemotherapy. The idea of a "cancer stem cell," an especially tough type of cell from the mutated clone, has been invoked to explain the reason for the regrowth of a tumor in an area that was treated with intense radiation. However, it's now clear that normal cells are attracted to an irradiated area.[5,6] The recognition of a "bystander effect," in which radiation (or other[7]) injury to one cell injures near-by cells by signals from the injured cell, has led to the recognition that ordinary stem cells or repair cells entering an area where a tumor has been destroyed will be modified by the residual damage of cells in the area. The ability to recruit normal cells into a damaged area, the "cancer field," the way normal organs do, shows that tumors can be thought of as organ-like structures, and that knowledge of the organizing principles of normal organs might improve our knowledge of tumors. The idea that cancer is primarily a problem of organization isn't new: Johannes Muller, in the 19th century, and J.W. Orr, and D.W. Smithers, in the 1940s and 1950s, and many others, have suggested that something outside of the individual cell could cause the disorganization.

Once it is accepted that cancer is a systemic disease, and that a tumor, or the place in the body where a tumor has been removed, is something more than a collection of defective cells, very different therapeutic approaches can be considered. Looking at the events in a failing heart, we can see that the potential repair cells recruited by the stressed heart are diverted by the conditions that they encounter there, and either die or

become connective tissue cells, secreting collagen, rather than becoming new muscle cells.

Something that everyone knows about tumors is that they are harder than the normal tissues in which they appear—they can be identified as lumps. Like the failing heart, they become harder than normal, and like the failing heart, the hardening can proceed to calcification. There has been general recognition that inflammation has a role in both heart disease and cancer, but the fact that chronic inflammation leads to fibrosis, and that fibrosis often leads to calcification, is still usually considered not to be relevant to understanding and treating cancer. The tissue hardness that allows oncologists to diagnose cancer[8] is ignored when choosing treatments, which isn't surprising, since treatments that destroy cancer cells increase the production of collagen.

Aspirin is commonly recommended for preventing heart attacks, because it helps to prevent abnormal blood clots, but it has other effects that are beneficial in heart disease, for example reducing the generalized fibrosis of the heart that develops after a heart attack.[9,10] It also protects against fibrosis in other organs, by a variety of mechanisms, and this effect on the extracellular matrix seems to be one of ways in which it protects against cancer. DCA, dichloroacetate, the drug that has been in the news in recent years because it can stop cancer growth, by restoring the oxidation of glucose and stopping the aerobic production of lactic acid, has been found to reduce the fibrosis of a failing heart, by the same mechanism, restoring glucose oxidation. In general, substances that increase collagen production are promoters of cancer and contribute to the progression of heart failure, and other degenerative changes.

The incidence of cancer increases exponentially with age, but when random mutations are seen as the cause of cancer, aging as an essential cause of cancer is disregarded. The total collagen content of the body increases with aging, and the stiffness of that collagen also increases. The total collagen content in cancer patients is higher than in people without cancer.[11] This suggests that the processes in the body that produce aging are acting more intensely in those who develop cancer. As the collagen accumulates in the extracellular matrix, the whole body becomes more favorable for the appearance of cancer.

Plastic surgeons have promoted the idea of injecting collagen into tissues with the argument that they are "replacing collagen lost with aging," but in fact collagen accumulates with aging. It is the greater

compactness and stiffness of collagen in old skin that produces noticeable changes such as wrinkling. The difference between calf skin leather, used for soft gloves and purses, and cow hide, used for shoe soles and boots, illustrates the changes that occur with aging. Supermarkets used to categorize chickens as fryers and stewers, or stewing hens. The difference was the age and toughness, very young chickens could be cooked quickly, old laying hens had accumulated more collagen, and especially the cross-linked hardened collagen, and required long cooking to reduce the toughness. Old beef animals are usually sold as cheaper stew meat or hamburger, because the age-hardened collagen can make a steak too rubbery to chew if it's quickly cooked.

In a healthy young organism, tissue injuries are repaired by processes reminiscent of Metchnikov's experiment in which he put a thorn into a jelly fish, and found that wandering cells, phagocytes, converged on the foreign object, surrounding it. If they couldn't eat it, they caused it to be expelled. The importance of that experiment was that it showed that injured tissues emit signals that attract certain types of cell. The process of removing damaged tissues by phagocytosis guides the formation of new tissue, starting with the secretion of collagen, which guides the maturation of the new cells.

Around the middle of the last century, Hans Selye experimented with the antiseptic implantation of a short piece of a narrow glass tube under the skin of rats. The irritation from the glass object caused a collagenous capsule to be formed around it, in the well known "foreign body reaction." He found that a filament of tissue formed in the center of the tube, connecting the two ends of the capsule. The isolated tissue of the filament quickly underwent the degenerative changes seen in aged connective tissues, but if he periodically removed the fluid around it, and allowed fresh lymph fluid to fill the capsule, the filament retained a youthful elasticity, even as the rat aged. Isolation from the organism caused age-like degeneration to develop rapidly. When the organism can't remove a foreign object, the collagenous capsule that encloses it has a high probability of forming a cancer. This "foreign body carcinogenesis" has been studied for many years.

Foreign body carcinogenesis is closely related to chemical carcinogenesis, radiation carcinogenesis, and hormonal carcinogenesis. Chemical carcinogens such as methylcholanthrene are irritating when injected, and stimulate collagen production. Neither type of carcinogenesis is

always effective, because this collagen reaction can be protective, by isolating the irritant toxin.[12] Radiation stimulates the secretion of collagen, and causes cross-linking that makes it stiffer, and slows its removal, leading to its accumulation.[13] Some types of cross-linking block the ability of macrophages to remove it, creating something like a diffuse foreign body reaction. Estrogen, for example in the process of causing breast cancer, causes increased collagen synthesis. This is widely recognized, in the association of "breast density" (a high collagen content) with the risk of cancer. Estrogen also causes the formation of the enzymes that cross-link and stiffen the collagen, lysyl oxidase and transglutaminase.[14–16]

Although ultraviolet and ionizing radiation can act directly on collagen, to stiffen it, the greatest effect of the radiation is probably by reaction with relatively unstable components of tissues, such as polyunsaturated fatty acids, which then react with the collagen, cross-linking it.[17] Even in the absence of radiation, a deficiency of vitamin E accelerates the spontaneous decomposition of the unsaturated fats, accelerating the aging of collagen.[18] Many observations suggest that all of the collagen-aging carcinogenic factors interact synergistically.

When cells are placed on a glass slide coated with collagen, they move to parts of the collagen that have been cross-linked, and they move from slightly cross-linked collagen to stiffer, more thoroughly cross-linked areas.[19] When they are on stiffer collagen, they pull themselves more tightly toward it, continuously expending energy in the process. The muscle-like contraction of the cell causes it to become more rigid.[8] The increased hardness of even small tumors makes it possible to identify lymph node metastases from a breast cancer by touch, without removing them.[20]

The increased energy cost of this "isotonic contraction" of the cell filaments requires more energy to sustain, and will tend to create lactic acid, the way intense muscle contraction does, while consuming oxygen at a higher rate. The increased lactic acid and decreased oxygen availability stimulate the synthesis of more collagen, the growth of new blood vessels, expression of enzymes for increasing the stiffness of the collagen, and other processes associated with inflammation, aging, and cancer. Blocking even one of these processes, the lysyl oxidase cross-linking enzyme, can reduce the invasiveness of a cancer.[21] Some observations[22] show that the circulating cells of metastatic cancer are more rigid than

other cells, which would increase the likelihood that they will block capillaries, creating oxygen-deprived nests of collagen-secreting cells.

One of the substances produced by stressed cells that's involved in tumor induction, growth, and metastasis[23–25] is the enzyme heme oxygenase, which breaks down the essential component of respiratory enzymes, heme, producing carbon monoxide as a product, which inhibits cell respiration, increasing reliance on the glycolysis which produces lactic acid. If metastatic cells continue to produce this enzyme, this is likely to contribute to reconstituting the "cancer field," with increased HIF, hypoxia inducible factor, and a variety of other regulatory agents, each of which has its protective functions elsewhere, but which in combination can worsen the tumor.

Substances that inhibit inflammation are likely to also inhibit excessive collagen synthesis, serotonin secretion, and the formation of estrogen. Besides aspirin, some effective substances are apigenin and naringenin, found in oranges and guavas. These flavonoids also inhibit the formation of nitric oxide and prostaglandins, which are important for inflammation and carcinogenesis.[26] Increased CO_2, which has a variety of anti-inflammatory effects, can decrease collagen formation and tissue collagen content significantly.[27]

Deprivation of glucose and oxygen, which can be the local result of a cellular environment of condensed, stiffened collagen and the cellular tension and activation produced in response, combined with systemic stress that causes free fatty acids to interfere with the oxidation of sugar, activates enzymes that can dissolve collagen (MMP-2 and MMP-9). These enzymes are involved in metastasis, allowing cells to escape from the condensed collagen, but although they are normally thought of as enzymes that act outside of cells, they can also enter the cell's nucleus, where they degrade the DNA, causing the mutations and chromosomal abnormalities that are so characteristic of cancer.[28] Like glucose deprivation, exposure to 2-deoxyglucose, often used in tumor imaging, promotes metastasis.[29]

The fact that cancer cells are stressed and damaged, and accumulate DNA damage, means that in a typical tumor there is a high rate of cell death. The number of apoptotic (disintegrating) cells in a tumor corresponds to the aggressiveness of the tumor.[30] In the 1940s and 1950s, Polezhaev demonstrated that dying cells stimulate cell renewal, and this is true in young and healthy organs, as well as in tumors.

In 36% of women who had had a breast removed, from 7 to 22 years previously, identifiable (by the same tests used to diagnose breast cancer) cancer cells could be found circulating in their blood stream.[31] Tissue biopsies would be able to find the sources of those circulating cells, nests of similar cells throughout the body, which were dying about as fast as they were replicating. In 1969, Harry Rubin described an autopsy study which found that everyone over the age of 50 had at least one diagnosable cancer in some tissue. "Occult microscopic cancers are exceedingly common in the general population and are held in a dormant state by a balance between cell proliferation and cell death and also an intact host immune surveillance."[32] These authors observed that the stress of surgery stimulates tumor growth, by various mechanisms, and that surgery increases the risk of developing cancer in apparently cancer-free patients.

In 1956, Hardin Jones wrote "If one has cancer and opts to do nothing at all, he will live longer and feel better than if he undergoes radiation, chemotherapy or surgery, other than when used in immediate life-threatening situations." In the 1990s, a group of cancer specialists were asked what they would do if they were diagnosed with prostate cancer, and most of them said they would do nothing.

The radical mastectomy, which removed massive amounts of apparently normal tissue as well as the breast tumor, was practiced for hundreds of years, and was the standard treatment for breast cancer until the 1980s, after G.W. Crile, Jr., had publicized the evidence showing that simply removing the tumor lump itself didn't cause a higher mortality rate, and that the surgery produced much less disability.

Although the lumpectomy was eventually accepted by the profession, the evidence that the long term survival rate was higher when the surgery was done during the luteal phase in premenopausal women has been generally ignored, because the cancer ideology maintains that the fate of the cancer is in the cells, rather than in the patient's hormone balance.

Because of the continual indoctrination about the importance of "early diagnosis to increase the chance of a cure," and the widely publicized "cure rates," it's easy for doctors to rush people into treatment, before they have time to study the issue. Dean Burk, who was a collaborator of Otto Warburg's for many years, was quoted in regard to the claims of the American Cancer Society that "They lie like scoundrels."

In the 1970s, I noticed that the definitions of the features of uterine cancer had been changed recently, including as "cancer" things that had previously been classified as merely abnormal or precancerous. Reading more about the grading of cancer, I saw that other cancers had been defined more inclusively since the 1940s. Things that had previously not been called cancer were now being counted among the cancers that were cured by the various treatments, so, necessarily, the rate of cure had increased. The true situation could be seen by the age-specific mortality rate for each type of cancer. During the period when the "cure rates" were increasing, the age-specific death rates had increased. I think that's the sort of thing that Dean Burk had in mind.

Nearly all of the studies of "cure rates" are comparisons of one ideologically-based and lucrative treatment against another ideologically-based and more or less lucrative treatment. When the cure rate, for example for breast cancer surgery, varies with the amount of progesterone in the body, there is very little interest in investigating the processes involved, because lucrative products aren't involved.

When abnormal "metastatic" cells circulate in the blood or lymph, most of them die spontaneously when they stick in a place that doesn't support their growth. Many of the nests of cells that have started to grow probably regress spontaneously when conditions in the body change. Even large, clearly diagnosed tumors occasionally regress spontaneously. Aging and sickness tend to support the vicious cycles that lead to the progressive deterioration of the collagenous matrix. Stress (even anxiety-induced hyperventilation) produces alkalosis, and alkalosis favors increased collagen synthesis, while lower pH inhibits it.[33] For example, within a minute or two of hyperventilating, platelets release serotonin, and serotonin is a major promoter of collagen synthesis and fibrosis.

The vicious cycles that promote cancer can be interrupted to some extent simply by reducing exposure to things that promote stress and inflammation—endotoxin, polyunsaturated fats, amino acid imbalance, nutritional deficiencies, ionizing radiation, estrogens—and maintaining optimal levels of things that protect against those—carbon dioxide, vitamin E, progesterone, light, aspirin, sugars, and thyroid hormone, for example.

The Dark Side of Stress (Learned Helplessness)

Ray Peat's Newsletter, 2016

LIVING is development; the choices we make create our individuality. If genetically identical mice grow up in a large and varied environment, small differences in their experience will affect cell growth in their brains, leading to large differences in their exploratory behavior as they age.[1] Geneticists used to say that "genes determine our limits," but this experiment shows that an environment can provide both limitations and opportunities for expanding the inherited potential. If our environment restricts our choices, our becoming human is thwarted, the way rats' potentials weren't discovered when they were kept in the standard little laboratory boxes. An opportunity to be complexly involved in a complex environment lets us become more of what we are, more humanly differentiated.

A series of experiments that started at the University of California in 1960 found that rats that lived in larger spaces with various things to explore were better at learning and solving problems than rats that were raised in the standard little laboratory cages.[2] Studying their brains, they found that the enzyme cholinesterase, which destroys the neurotransmitter, acetylcholine, was increased. They later found that the offspring of these rats were better learners than their parents, and their brains contained more cholinesterase. Their brains were also larger, with a considerable thickening of the cortex, which is considered to be the part mainly responsible for complex behavior, learning and intelligence.

These processes aren't limited to childhood. For example, London taxi drivers who learn all the streets in the city develop a larger hippocampus, an area of the brain involved with memory.

The 1960s research into environmental enrichment coincided with political changes in the U.S., but it went against the dominant scientific ideas of the time. Starting in 1945, the U.S. government had begun

The autonomic nervous system has traditionally been divided into the sympathetic-adrenergic system, and the parasympathetic-cholinergic system, with approximately opposing functions, intensifying energy expenditure and limiting energy expenditure, respectively. The hormonal system and the behavioral system interact with these systems, and each is capable of disrupting the others. Disruptive factors in the environment have increased in recent decades.

a series of projects to develop techniques of behavior modification or mind control, using drugs, isolation, deprivation, and torture. In the 1950s, psychiatry often used lobotomies (about 80,000, before they were generally discontinued in the 1980s) and electroconvulsive "therapy," and university psychologists tortured animals, often as part of developing techniques for controlling behavior.

The CIA officially phased out their MK Ultra program in 1967, but that was the year that Martin Seligman, at the University of Pennsylvania, popularized the idea of "learned helplessness." He found that when an animal was unable to escape from torture, even for a very short time, it would often fail to even try to escape the next time it was tortured. Seligman's lectures have been attended by psychologists who worked at Guantanamo, and he recently received a no-bid Pentagon grant of $31,000,000, to develop a program of "comprehensive soldier fitness," to train marines to avoid learned helplessness.

Curt Richter already in 1957 had described the "hopelessness" phenomenon in rats ("a reaction of hopelessness is shown by some wild rats very soon after being grasped in the hand and prevented from moving. They seem literally to give up,") and even how to cure their hopelessness, by allowing them to have an experience of escaping once.[3] Rats which would normally be able to keep swimming in a tank for two or three days, would often give up and drown in just a few minutes, after having an experience of "inescapable stress." Richter made the important discovery that the hearts of the hopeless rats slowed down before they died, remaining relaxed and filled with blood, revealing the dominant activity of the vagal nerve, secreting acetylcholine.

The sympathetic nervous system (secreting noradrenaline) accelerates the heart, and is usually activated in stress, in the "fight or flight" reaction, but this radically different (parasympathetic) nervous activity hadn't previously been seen to occur in stressful situations. The parasympathetic, cholinergic, nervous system had been thought of as inactive during stress, and activated to regulate processes of digestion, sleep, and repair. Besides the cholinergic nerves of the parasympathetic system, many nerves of the central nervous system also secrete acetylcholine, which activates smooth muscles, skeletal muscles, glands, and other nerves, and also has some inhibitory effects. The parasympathetic nerves also secrete the enzyme, cholinesterase, which destroys acetylcholine.

However, many other types of cell (red blood cells, fibroblasts, sympathetic nerves, marrow cells), maybe all cells, can secrete cholinesterase.

Because cholinergic nerves have been opposed to the sympathetic, adrenergic, nerves, there has been a tendency to neglect their nerve exciting roles, when looking at causes of excitotoxicity, or the stress-induced loss of brain cells. Excessive cholinergic stimulation, however, can contribute to excitotoxic cell death, for example when it's combined with high cortisol and/or hypoglycemia.

Drugs that block the stimulating effects of acetylcholine (the anticholinergics) as well as chemicals that mimic the effects of acetylcholine, such as the organophosphate insecticides, can impair the ability to think and learn. This suggested to some people that age-related dementia was the result of the deterioration of the cholinergic nerves in the brain. Drugs to increase the stimulating effects of acetylcholine in the brain (by inactivating cholinesterase) were promoted as treatment for Alzheimer's disease.

Although herbal inhibitors were well known, profitable new drugs, starting with Tacrine, were put into use. It was soon evident that Tacrine was causing serious liver damage, but wasn't slowing the rate of mental deterioration.

As the failure of the cholinergic drug Tacrine was becoming commonly known, another drug, amantadine (later, the similar memantine) was proposed for combined treatment. In the 1950s, the anticholinergic drug atropine was proposed a few times for treating dementia, and amantadine, which was also considered anticholinergic, was proposed for some mental conditions, including Creutzfeldt-Jacob Disease.[4] It must have seemed odd to propose that an anticholinergic drug be used to treat a condition that was being so profitably treated with a pro-cholinergic drug, but memantine came to be classified as an anti-excitatory "NMDA blocker," to protect the remaining cholinergic nerves, so that both drugs could logically be prescribed simultaneously. The added drug seems to have a small beneficial effect, but there has been no suggestion that this could be the result of its previously-known anticholinergic effects.

Over the years, some people have suspected that Alzheimer's disease might be caused partly by a lack of purpose and stimulation in their life, and have found that meaningful, interesting activity could improve their mental functioning. Because the idea of a "genetically determined hard-wired" brain is no longer taught so dogmatically, there is increasing

interest in this therapy for all kinds of brain impairment. The analogy to the Berkeley enrichment experience is clear, so the association of increasing cholinesterase activity with improving brain function should be of interest.

The after-effect of poisoning by nerve gas or insecticide has been compared to the dementia of old age. The anticholinergic drugs are generally recognized for protecting against those toxins. Traumatic brain injury, even with improvement in the short term, often starts a long-term degenerative process, greatly increasing the likelihood of dementia at a later age. A cholinergic excitotoxic process is known to be involved in the traumatic degeneration of nerves,[5] and the use of anticholinergic drugs has been recommended for many years to treat traumatic brain injuries.[6]

In 1976 there was an experiment[7] that made an important link between the enrichment experiments and the learned helplessness experiments. The control animals in the enrichment experiments were singly housed, while the others shared a larger enclosure. In the later experiment, it was found that the rats "who were reared in isolation died suddenly when placed in a stressful swimming situation," while the group-housed animals were resistant, effective swimmers. Enrichment and deprivation have very clear biological meaning, and one is the negation of the other.

The increase of cholinesterase, the enzyme that destroys acetylcholine, during enrichment, serves to inactivate cholinergic processes. If deprivation does its harm by increasing the activity of the cholinergic system, we should expect that a cholinergic drug might substitute for inescapable stress, as a cause of learned helplessness, and that an anticholinergic drug could cure learned helplessness. Those tests have been done: "Treatment with the anticholinesterase, physostigmine, successfully mimicked the effects of inescapable shock." "The centrally acting anticholinergic scopolamine hydrobromide antagonized the effects of physostigmine, and when administered prior to escape testing antagonized the disruptive effects of previously administered inescapable shock."[8]

This kind of experiment would suggest that the anticholinesterase drugs still being used for Alzheimer's disease treatment aren't biologically helpful. In an earlier newsletter I discussed the changes of growth hormone, and its antagonist somatostatin, in association with dementia:

Growth hormone increases, somatostatin decreases. The cholinergic nerves are a major factor in shifting those hormones in the direction of dementia, and the anticholinergic drugs tend to increase the ratio of somatostatin to growth hormone. Somatostatin and cholinesterase have been found to co-exist in single nerve cells.[9]

Estrogen, which was promoted so intensively as prevention or treatment for Alzheimer's disease, was finally shown to contribute to its development. One of the characteristic effects of estrogen is to increase the level of growth hormone in the blood. This is just one of many ways that estrogen is associated with cholinergic activation. During pregnancy, it's important for the uterus not to contract. Cholinergic stimulation causes it to contract; too much estrogen activates that system, and causes miscarriage if it's excessive. An important function of progesterone is to keep the uterus relaxed during pregnancy. In the uterus, and in many other systems, progesterone increases the activity of cholinesterase, removing the acetylcholine which, under the influence of estrogen, would cause the uterus to contract.

Progesterone is being used to treat brain injuries, very successfully. It protects against inflammation, and in an early study, compared to placebo, lowered mortality by more than half. It's instructive to consider its anticholinergic role in the uterus, in relation to its brain protective effects. When the brain is poisoned by an organophosphate insecticide, which lowers the activity of cholinesterase, seizures are likely to occur, and treatment with progesterone can prevent those seizures, reversing the inhibition of the enzyme (and increasing the activity of cholinesterase in rats that weren't poisoned).[10] Similar effects of progesterone on cholinesterase occur in menstrually cycling women,[11] implying that this is a general function of progesterone, not just something to protect pregnancy. Estrogen, with similar generality, decreases the activity of cholinesterase. DHEA, like progesterone, increases the activity of cholinesterase, and is brain protective.[12]

Brain trauma consistently leads to decreased activity of this enzyme,[13] causing the acetylcholine produced in the brain to accumulate, with many interesting consequences. In 1997, a group[14] created brain injuries in rats to test the idea that a cholinesterase inhibitor would improve their recovery and ability to move through a maze. They found instead that it reduced the cognitive ability of both the injured and normal rats. An anticholinergic drug, selegeline (deprenyl) that is used

to treat Parkinson's disease and, informally, as a mood altering antiaging drug, was found by a different group[15] to improve cognitive recovery from brain injuries.

One of acetylcholine's important functions, in the brain as elsewhere, is the relaxation of blood vessels, and this is done by activating the synthesis of NO, nitric oxide.[16] The basic control of blood flow in the brain is the result of the relaxation of the wall of blood vessels in the presence of carbon dioxide, which is produced in proportion to the rate at which oxygen and glucose are being metabolically combined by active cells. In the inability of cells to produce CO_2 at a normal rate, nitric oxide synthesis in blood vessels can cause them to dilate. The mechanism of relaxation by NO is very different, however, involving the inhibition of mitochondrial energy production.[17] Situations that favor the production and retention of a larger amount of carbon dioxide in the tissues are likely to reduce the basic "tone" of the parasympathetic nervous system, as there is less need for additional vasodilation.

Nitric oxide can diffuse away from the blood vessels, affecting the energy metabolism of nerve cells.[18] Normally, astrocytes protect nerve cells from nitric oxide,[19] but that function can be altered, for example by bacterial endotoxin absorbed from the intestine[20] or by amyloid-beta,[21] causing them to produce nitric oxide themselves.

Nitric oxide is increasingly seen as an important factor in nerve degeneration.[22] Nitric oxide activates processes[23] that can lead to cell death. Inhibiting the production of nitric oxide protects against various kinds of dementia.[24,25] Brain trauma causes a large increase in nitric oxide formation, and blocking its synthesis improves recovery.[26,27] Organophosphates increase nitric oxide formation, and the protective anticholinergic drugs such as atropine reduce it.[28,29] Stress, including fear[30] and isolation[31] can activate the formation of nitric oxide, and various mediators of inflammation also activate it. The nitric oxide in a person's exhaled breath can be used to diagnose some diseases, and it probably also reflects the level of their emotional well-being.

The increase of cholinesterase by enriched living serves to protect tissues against an accumulation of acetylcholine. The activation of nitric oxide synthesis by acetylcholine tends to block energy production, and to activate autolytic or catabolic processes, which are probably involved in the development of a thinner cerebral cortex in isolated or stressed ani-

mals. Breaking down acetylcholine rapidly, the tissue renewal processes are able to predominate in the enriched animals.

Environmental conditions that are favorable for respiratory energy production are protective against learned helplessness and neurodegeneration, and other biological problems that involve the same mechanisms. Adaptation to high altitude, which stimulates the formation of new mitochondria and increased thyroid (T_3) activity, has been used for many years to treat neurological problems, and the effect has been demonstrated in animal experiments.[32] Bright light can reverse the cholinergic effects of inescapable stress.[33]

During the development of learned helplessness, the T_3 level in the blood decreases,[34] and removal of the thyroid gland creates the "escape deficit," while supplementing with thyroid hormone before exposing the animal to inescapable shock prevents its development.[35] After learned helplessness has been created in rats, supplementing with T_3 reverses it.[36,37]

Hypothyroidism and excess cholinergic tone have many similarities, including increased formation of nitric oxide, so that similar symptoms, such as muscle inflammation, can be produced by cholinesterase inhibitors such as Tacrine, by increased nitric oxide, or by simple hypothyroidism.[38,39]

Insecticide exposure has been suspected to be a factor in the increased incidence of Alzheimer's disease,[40] but it could be contributing to many other problems, involving inflammation, edema, and degeneration. Another important source of organophosphate poisoning is the air used to pressurize airliners, which can be contaminated with organophosphate fumes coming from the engine used to compress it.

Possibly the most toxic component of our environment is the way the society has been designed, to eliminate meaningful choices for most people. In the experiment of Freund, et al., some mice became more exploratory because of the choices they made, while others' lives became more routinized and limited. Our culture reinforces routinized living. In the absence of opportunities to vary the way you work and live to accord with new knowledge that you gain, the nutritional, hormonal and physical factors have special importance.

Supplements of thyroid and progesterone are proven to be generally protective against the cholinergic threats, but there are many other factors that can be adjusted according to particular needs. Niacinamide,

like progesterone, inhibits the production of nitric oxide, and also like progesterone, it improves recovery from brain injury.[41] In genetically altered mice with an Alzheimer's trait, niacinamide corrects the defect.[42] Drugs such as atropine and antihistamines can be used in crisis situations. Bright light, without excess ultraviolet, should be available every day.

The cholinergic system is much more than a part of the nervous system, and is involved in cell metabolism and tissue renewal. Most people can benefit from reducing intake of phosphate, iron, and polyunsaturated fats,[43] and from choosing foods that reduce production and absorption of endotoxin. And, obviously, drugs that are intended to increase the effects of nitric oxide (asparagine, zildenafil/Viagra, minoxidil/Rogaine) and acetylcholine (bethanechol, benzpyrinium, etc.) should be avoided.

The Great Fish Oil Experiment

Ray Peat's Newsletter, 2007

READING medical journals and following the mass media, it's easy to get the idea that fish oil is something any sensible person should use. It's rare to see anything suggesting that it could be dangerous.

During the recent years in which the U.S. government has gone from warning against the consumption of too much of these omega-3 oils ("to assure that the combined daily intake of two fatty acids that are components" "(i.e., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) would not exceed 3 g per person per day (g/p/d)") to sponsoring biased industry claims, there has been considerable accumulation of information about the dangers of fish oils and omega-3 fatty acids. But there has been an even greater increase in the industry's promotional activities.

The U.S. government and the mass media selectively promote research that is favorable to the fish oil industry. The editorial boards of oil research journals often include industry representatives, and their editorial decisions favor research conclusions that promote the industry, in the way that editorial decisions in previous decades favored articles that denied the dangers of radiation and reported that estrogen cures almost everything. Marcia Angell, former editor of the *NEJM*, has observed that the "significant results" reported in published studies can be properly interpreted only by knowing how many studies reporting opposite results were rejected by the editors.

One way to evaluate published studies is to see whether they tell you everything you would need to know to replicate the experiment, and whether the information they provide is adequate for drawing the conclusions they draw, for example whether they compared the experimental subjects to proper control subjects. With just a few minimal critical principles of this sort, most "scientific" publications on nutrition, endocrinology, cancer and other degenerative diseases are seen to be unscientific. In nutritional experiments with fish oil, controls must receive similar amounts of vitamins A, D, E, and K, and should include fat free or "EFA" deficient diets for comparison.

In declaring EPA and DHA to be safe, the FDA neglected to evaluate their antithyroid, immunosuppressive, lipid peroxidative,[1] light

sensitizing, and antimitochondrial effects, their depression of glucose oxidation,[2] and their contribution to metastatic cancer,[3] lipofuscinosis and liver damage, among other problems.

> *"Houston-based Omega Protein Inc.'s bottom line may get a little fatter.*
>
> *The publicly traded company, which produces an Omega-3 fatty acid product called OmegaPure, has signed an agreement to provide its fish oil in school lunches in 38 school districts in South Texas beginning this month.*
>
> *The 500-person company, which has ties to former President George Bush's Zapata Corp., will distribute the product through an agreement with Mercedes-based H&H Foods.*
>
> *Although the dollar amount of the contract between Omega Protein and H&H Foods hinges on future sales, the company is poised to cash in as school administrators and parents refocus their attention on the nutritional content of student diets.*
>
> *Omega Protein President and CEO Joseph von Rosenberg says the company's recent investment of $16.5 million for a fish oil refinery in Reedville, Va., scheduled for completion in May, and an increased awareness of the benefits of Omega-3 in human food, positions Omega to capitalize on predicted demand."*
>
> *Jenna Colley*
>
> *Houston Business Journal*

Andrew Weil was on the radio recently recommending DHA (usually found in fish oil[†]) to treat depression, and I think that means that a lot of people are buying it and eating it. A few years ago the government declared that it was "generally regarded as safe" and approved its use in baby formula, and a few months ago Texas school districts contracted with Omega Protein (which grew out of the Bush family's Zapata Corporation) to provide menhaden fish oil for school lunches. Between the 1950s and the 1970s, people were assured that eating polyunsaturated seed oils would protect them against heart disease. There's no evidence

that the bad outcome of that campaign decreased the gullibility of the public. They are happily joining in the latest public health experiment.

When a group of people in government and industry decide on a policy, they can use carrots (good jobs, grants, and prestige) and sticks (loss of jobs and grants, organized slander, and worse) to make their guidelines clear, and most people will choose to follow those cues, even if they know that the policy is wrong. Historically, policy makers have told the public that "radiation is good for you," "estrogen will make you fertile (or safely infertile) and feminine and strong and intelligent," "starchy foods will prevent diabetes and obesity," "using diuretics and avoiding salt will make pregnancy safer," and that the polyunsaturated fatty acids are "nutritionally essential, and will prevent heart disease."

The original "essential fatty acids" were linoleic, linolenic, and arachidonic acids. Now that the toxic effects of those are coming to be recognized, new "essential fatty acids," the omega-3 fatty acids, including those with long chains, found in fish oils, are said to make babies more intelligent, to be necessary for good vision, and to prevent cancer, heart disease, obesity, arthritis, depression, epilepsy, psychosis, dementia, ulcers, eczema and dry skin.

With just a normal amount of vitamin E in the diet, cod liver oil is certain to be highly oxidized in the tissues of a mammal that eats a lot of it, and an experiment with dogs showed that it could increase their cancer mortality from the normal 5 % to 100 %. Although fish oils rapidly destroy vitamin E in the body, some of them, especially the liver oils, can provide useful vitamins, A and D. In studies comparing fish oil diets with standard diets, these nutrients, as well as any toxins besides fatty acids[4,5] in either type of oil, should be taken into account, but they seldom are.

Despite the nutritional value of those vitamins, fish oils are generally much more immunosuppressive than the seed oils, and the early effects of fish oil on the "immune system" include the suppression of prostaglandin synthesis, because the more highly unsaturated long chain fats interfere with the conversion of linoleic acid into arachidonic acid and prostaglandins. The prostaglandins are so problematic that their

† Weil recommends eating "oily fish"—"wild Alaskan salmon, mackerel, sardines, or herring." "If you do take supplements, fish oil is a better source of DHA than algae."

suppression is helpful, whether the inhibition is caused by aspirin or vitamin E, or by fish oil.

Some of the important antiinflammatory effects of fish oil result from the oxidized oils, rather than the unchanged oils.[6,7] These oils are so unstable that they begin to spontaneously oxidize even before they reach the bloodstream.

In experiments that last just a few weeks or months, there may not be time for cancers to develop, and on that time scale, the immunosuppressive and antiinflammatory effects of oxidized fish oil might seem beneficial. For a few decades, x-ray treatments were used to relieve inflammatory conditions, and most of the doctors who promoted the treatment were able to retire before their patients began suffering the fatal effects of atrophy, fibrosis, and cancer. (But a few people are still advocating x-ray therapy for inflammatory diseases.[8]) The fish oil fad is now just as old as the x-ray fad was at its peak of popularity, and if its antiinflammatory actions involve the same mechanisms as the antiinflammatory immunosuppressive x-ray treatments, then we can expect to see another epidemic of fibrotic conditions and cancer in about 15 to 20 years.

Around 1970 researchers reported that animals given fish oil in their food lived longer than animals on the standard diet. Alex Comfort, who was familiar with the research showing that simple reduction of food intake increased longevity, observed that the animals were very reluctant to eat the food containing smelly fish oil, and were eating so little food that their longevity could be accounted for by their reduced caloric intake. Even when "fresh" deodorized fish oil is added to the diet, its spontaneous oxidation before it reaches the animal's tissues reduces its caloric value. Without antioxidants, fish oil is massively degraded within 48 h, and even with a huge amount of antioxidant there is still considerable degradation.[9,10]

Fish oil has been used for hundreds of years as varnish or for fuel in lamps, and the fatty fish have been used as fertilizer and animal feed, and later the hydrogenated solid form of the oil, which is more stable, has been used in Europe as a food substitute for people. When whale hunting was reduced around 1950, fish oil was substituted for whale oil in margarine production. Like the seed oils, such as linseed oil, the fish oils were mostly replaced by petroleum derivatives in the paint industry after the 1960s.

Although by 1980 many animal diseases were known to be caused by eating oily fish, and the unsaturated oils were known to accelerate the formation of the "age pigment," lipofuscin, many "beneficial effects" of dietary fish oil started appearing in research journals around that time, and the mass media, responding to the industry's public relations campaign, began ignoring studies that showed harmful effects from eating fish oil.

When reviewers in professional journals begin to ignore valid research whose conclusions are harmful to the fish oil industry, we can see that the policy guidelines set by the industry and its agents in government have become clear. Around the end of the century, we begin to see a strange literary device appearing, in which research reports on the toxic effects of omega-3 oils are prefaced by remarks to the effect that "we all know how great these oils are for good health." I think I detect groveling and shuffling of the feet by authors who want to get their work published. If you are willing to say that your work probably doesn't mean what it seems to mean, maybe they will publish it.

For more than 50 years, the great majority of the medical publications on estrogen were part of the drug industry's campaign to fraudulently gain billions of dollars, and anyone who cared to analyze them could see that the authors and editors were part of a cult, rather than seekers of useful knowledge. Likewise, the doctrine of the harmlessness of x-rays and radioactive fallout was kept alive for several decades by demonizing all who challenged it. It now looks as though we are in danger of entering another period of medical-industrial-governmental cultism, this time to promote the universal use of polyunsaturated fats as both drugs and foods.

In 2004, a study of 29,133 men reported that the use of omega-3 oil or consumption of fish didn't decrease depression or suicide, and in 2001, a study of 42,612 men and women reported that after more than 9 years the use of cod liver oil showed no protective effect against coronary heart disease.[11,12]

The most popular way of arguing that fish oil will prevent heart disease is to show that it lowers blood lipids, continuing the old approach of the American Heart Association's "heart protective diet." Unfortunately for that argument, it's now known that the triglycerides in the blood are decreased because of the fish oil's toxic effects on the liver.[13,14] In experiments with rats, EPA and DHA lowered blood lipids only when

given to rats that had been fed, in which case the fats were incorporated into tissues, and suppressed mitochondrial respiration.[15]

The belief that eating cholesterol causes heart disease was based mainly on old experiments with rabbits, and subsequent experiments have made it clear that it is oxidized cholesterol that damages the arteries.[16] Since both fish oil and oxidized cholesterol damage rabbits' arteries, and since the lipid peroxides associated with fish oil attack a great variety of biological materials, including the LDL lipoproteins carrying cholesterol, the implications of the rabbit experiments now seem very different.

Another way of arguing for the use of fish oil or other omega-3 fats is to show a correlation between disease and a decreased amount of EPA, DHA, or arachidonic acid in the tissues, and to say "these oils are deficient, the disease is caused by a deficiency of essential fatty acids." Those oils are extremely susceptible to oxidation, so they tend to spontaneously disappear in response to tissue injury, cellular excitation, the increased energy demands of stress, exposure to toxins or ionizing radiation, or even exposure to light. That spontaneous oxidation is what made them useful as varnish or paint medium. But it is what makes them sensitize the tissues to injury. Their "deficiency" in the tissues frequently corresponds to the intensity of oxidative stress and lipid peroxidation; it is usually their presence, rather than their deficiency, that created the disposition for the disease.

One of the earliest harmful effects of polyunsaturated fatty acids, PUFA, to be observed was their acceleration of the formation of lipofuscin or ceroid, the "age pigment," during oxidative stress or vitamin E deficiency. Associated with the formation of lipofuscin, the PUFA were discovered to cause degeneration of the gonads and brain, and the fact that vitamin E could prevent some of their toxic effects led to the idea that vitamin E was essentially an antioxidant. Unfortunately, the protective effect of vitamin E against the PUFA is only partial.[17]

The degenerative diseases are all associated with disturbances involving fat metabolism and lipid peroxidation. Alzheimer's disease, alcoholic and nonalcoholic liver disease, retinal degeneration, epilepsy, AIDS, diabetes, and a variety of circulatory problems involve breakdown products of the PUFA. The products of PUFA decomposition include acrolein, malondialdehyde, hydroxynonenal, crotonaldehyde, ethane, pentane, and the neuroprostanes, which are prostaglandin-like molecules formed

from DHA by free radical lipid peroxidation products, especially in the brain and at a higher level in Alzheimer's disease.

The reactions of three types of cell—vascular endothelium, nerve cells, and thymus cells—to the PUFA will illustrate some of the important processes involved in their toxicity.

When the body doesn't have enough glucose, free fatty acids are released from the tissues, and their oxidation blocks the oxidation of glucose even when it becomes available from the breakdown of protein caused by cortisol, which is released during glucose deprivation. Cells of the thymus are sensitive to glucose deprivation, and even in the presence of glucose, cortisol prevents them from using glucose, causing them to take up fatty acids. The thymic cells die easily when exposed either to excess cortisol, or deficient glucose. The polyunsaturated fatty acids linoleate, arachidonate, and eicosapentaenoic, are especially toxic to thymic cells by preventing their inactivation of cortisol, increasing its action.[10,18,19] Lymphocytes from people with AIDS and leukemia are less able to metabolize cortisol. An extract of serum from AIDS patients caused lymphocytes exposed to cortisol to die 7 times faster than cells from healthy people. AIDS patients have high levels of both cortisol and free polyunsaturated fatty acids.[20]

The cytotoxicity caused by EPA and its metabolites (15 mg of EPA per liter killed over 90 % of a certain type of macrophage) isn't inhibited by vitamin E.[21] Immunological activation tends to kill T cells that contain PUFA.[22]

When animals are fed fish oil and then exposed to bacteria, their immunosuppressed thymic (T) cells cause them to succumb to the infection more easily than animals fed coconut oil or a fat free diet. Natural killer cells, which eliminate cancer cells and virus infected cells, are decreased after eating fish oil, and T suppressor cells are often increased. More subtle interference with immunity is produced by the actions of PUFA on the "immune synapse," a contact between cells that permits the transmission of immunological information. The immunosuppressive effect of fish oil is recognized as a useful aid in preventing the rejection of transplanted organs, but some studies are showing that survival a year after transplantation isn't improved.

Polyunsaturated fatty acids, especially those that can be turned into prostaglandins, are widely involved in causing inflammation and vascular leakiness. EPA and DHA don't form ordinary prostaglandins,

though the isoprostanes and neuroprostanes they produce during lipid peroxidation behave in many ways like the more common prostaglandins, and their enzymically formed eicosanoids have some functions similar to those of the common prostaglandins. The brain contains a very high concentration of these unstable fatty acids, and they are released in synapses by ordinary excitatory process.

Chan, et al., 1983,[23] found that polyunsaturated fats caused brain swelling and increased blood vessel permeability. In 1988, Chan's group found that DHA and other polyunsaturated fatty acids added to cultured cells from the cerebral cortex produced free radicals and stimulated production of malondialdehyde and lactate, and inhibited the uptake of glutamic acid, which suggests that they would contribute to prolonged excitation of the nerves.[24] In brain slices, the polyunsaturated fatty acids caused the production of free radicals and swelling of the tissue, and the saturated fatty acids didn't.[25] The PUFA inhibited the respiration of mitochondria in brain cells,[26] and at a higher concentration, caused them to swell,[27] but saturated fatty acids didn't produce edema. Free radical activity was shown to cause the liberation of free fatty acids from the cellular structure.[28,29] The activation of lipases by free radicals and lipid peroxides, with the loss of potassium from the cells, suggests that excitation can become a self-stimulating process, leading to cellular destruction.

DHA itself, rather than its decomposition products, facilitates excitatory (glutamate) nerve transmission,[30] and that excitatory action causes the release of arachidonic acid.[31]

Considering just one of the products of fish oil peroxidation, acrolein, and a few of its effects in cells, we can get an idea of the types of damage that could result from increasing the amount of omega-3 fats in our tissues.

The "barrier" between the brain and blood stream is one of the most effective vascular barriers in the body, but it is very permeable to oils, and lipid peroxidation disrupts it, damaging the ATPase that regulates sodium and potassium.[32] Apparently, anything that depletes the cell's energy, lowering ATP, allows an excess of calcium to enter cells, contributing to their death.[33] Increasing intracellular calcium activates phospholipases, releasing more polyunsaturated fats[34] The acrolein which is released during lipid peroxidation inhibits mitochondrial function by poisoning the crucial respiratory enzyme, cytochrome oxidase, resulting

in a decreased ability to produce energy.[35] (In the retina, the PUFA contribute to light-induced damage of the energy producing ability of the cells,[36] by damaging the same crucial enzyme.) Besides inhibiting the ability of nerve cells to produce energy from the oxidation of glucose, acrolein inhibits the ability of cells to regulate the excitatory amino acid glutamate,[37] contributing to the excitatory process. High levels of acrolein (and other products of PUFA degradation) are found in the brain in Alzheimer's disease.[38]

The "prion" diseases, CJD and TSE/BSE (mad cow disease) have many features in common with Alzheimer's disease, and several studies have shown that the "prion" protein produces its damage by activating the lipases that release polyunsaturated fatty acids and produce lipid peroxides.[39,40]

Acrolein reacts with DNA, causing "genetic" damage, and also reacts with the lysine in proteins, for example contributing to the toxicity of oxidized low density lipoproteins (LDL), the proteins that carry cholesterol and that became famous because of their involvement in the development of atherosclerosis that was supposedly caused by eating saturated fats.

My newsletter on mad cow disease discussed the evidence incriminating the use of fish meal in animal feed, as a cause of the degenerative brain diseases, and earlier newsletters (glycemia, and glycation) discussed the reasons for thinking that inappropriate glycation of lysine groups in proteins, as a result of a lack of protective carbon dioxide/carbamino groups, produces the amyloid (or "prion") proteins that characterize the dementias. Acrolein, produced from the decomposing "fish oils" in the brain, is probably the most reactive product of lipid peroxidation in the brain, and so would be likely to cause the glycation of lysine in the plaque-forming proteins.

These toxic effects of acrolein in the brain are analogous to the multitude of toxic effects of the omega-3 fatty acids and their breakdown products in all of the other organs and tissues of the body. Cancer cells are unusual in their degree of resistance to the lethal actions of the lipid peroxides, but the inflammatory effects of the highly unsaturated fatty acids are now widely recognized to be essentially involved in the process of cancerization (my newsletters on cancer and leakiness discuss some of the ways the fats are involved in tumor development).

The fats that we synthesize from sugar, or coconut oil, or oleic acid, the omega-9 series, are protective against the inflammatory PUFA, in some cases more effective even than vitamin E.

In Woody Allen's 1973 movie, Sleeper, the protagonist woke up after being frozen for 200 years, to find that saturated fats were health foods. At the time the movie was made, that had already been established (e.g., Hartroft and Porta,[41] who showed that adequate saturated fat in the diet helped to protect against the formation of lipofuscin).

> Royal Society for the Protection of Birds says 2004 has been the most catastrophic breeding season on record for seabirds along UK coasts. It says industrial fishing to supply fish meal and oil is barely sustainable and imperils the whole marine food web.
>
> "The UK has suffered serious seabird disasters this year already. In Shetland and Orkney, entire colonies of birds failed to produce any young because of severe food shortages." "On top of that, hundreds of seabirds have been washing ashore having perished at sea. Again, lack of food is thought to be one of the reasons." The report, Assessment Of The Sustainability Of Industrial Fisheries Producing Fish Meal And Fish Oil, was compiled for the RSPB by Poseidon Aquatic Resource Management Ltd and the University of Newcastle-upon-Tyne.

The Problem of Alzheimer's Disease as a Clue to Immortality

Ray Peat's Newsletter, 2006

I. Introduction

THE toxicity of estrogen and of the unsaturated fats has been known for most of the twentieth century, and much has been learned about their interactions in the aging process. The body, during this time, has been understood as a dynamic interaction of cellular trophic influences which govern both form and function. My argument here will be that some of our adaptive, protective regulatory processes are overridden by the excessive supply of unsaturated fats—supported by a few other toxins—in our diet, acting as a false-signal system, and that cholesterol, pregnenolone, and progesterone which are our main long-range defenses, are overcome by the effects of the unsaturated fats, and that the resulting cascade of ineffective and defective reactions (including various estrogen-stimulated processes) leads to lower and lower energy production, reduced function, and death. At certain times, especially childhood and old age, iron (which also has important regulatory roles) accumulates to the point that its signal functions may be inappropriate.

It interacts with estrogen and unsaturated fats in ways that can change restraint and adaptation into sudden self-destruction, apoptotic cell death. If we look at the human organism from one perspective, it seems coherent and intelligible, but from the perspective of established academic biological doctrine, it seems appallingly complex, lacking any visible integrating principle, and as a result simplistic mechanical, pharmaceutical, or religious ideas are increasingly offered to fill the gap. But experimental data can be taken out of the muddle, and put to coherent human use. In what follows, I am acting as though the doctrines of genetic determination and regulation by membranes were mere historical relics. The emerging control systems are now clear enough that we can begin to use them to reverse the degenerative diseases: Alzheimer's dementia, epileptic dementia, arthritis, osteoporosis, depression, hypertension, hardening of the heart and blood vessels, diabetes, and some types of tumor, immunodeficiencies, reflex problems,

and special atrophic problems, including clearing of amyloid and mucoid deposits. I think many people experience regenerative age-regressing when many circumstances are just right; for example, taking a trip to the mountains in the spring with friends can optimize several basic regulatory systems.

II. Common Factors in Brain Injury During Growth and Aging

Most people are surprised by the number of cells in the prenatal brain, and in the very old brain: In the human fetus at 6 months of development, there are about twice as many brain cells as there are at the time of birth, and in old age the number of cells in the brain keeps increasing with age, so that at the age of 90 the amount of DNA in the brain (36.94 g) is about 50 % greater than at the age of 16-20 (23.04 g). In the aged brain, glial cells multiply while neurons die. In the fetus, the cells that die are apparently nerve cells that haven't yet matured. The factors that are known to reduce the brain size at birth are also factors that are involved in the degenerating brain in old age or Alzheimer's disease: lack of oxygen, excess unsaturated fats or deficiency of saturated fats, estrogen excess, progesterone deficiency, and lack of glucose. A lack of carbon dioxide is probably harmful in both. Inflammation and blood clots may be factors in the aging brain, and bleeding with vascular spasm is sometimes a contributing factor to brain damage in both the old and the fetal brain. Endotoxemia may be a factor in nerve degeneration only during adult life, but it is sometimes present during pregnancy.[1,2]

III. A View of Entropy: Renewal of the Brain

When a fertilized egg is developing into a person, each cell division creates a new environment for the daughter cells, to which they adapt. They may run into limits and resistances (sometimes a certain gene doesn't meet the need of the situation, or toxins are present, or nutrients and hormones are imperfectly supplied), but the process is flexible, and a way is normally found to get around the limitation. The embryo's brain development is my favorite example of the ways genes interact with the environment. We might think of the "optimal brain development" of a person, or a rat, or a chicken, as something which is clearly limited

by "the genes." But if rats are given a stimulating environment, each generation gets a slightly bigger, slightly more intelligent brain. If rats are treated during pregnancy to increase the amount of progesterone, the offspring have bigger brains and learn more efficiently. Still, that might just be restoring a condition that was natural for rats in some perfect environment. Chickens develop inside an egg shell, and so the nutrients needed for their development are all present when the egg is laid.

The brain, like the other organs, stops growing when the food supply is used up. But an experimenter (Zamenhof) opened the egg shells at the stage of development when the brain normally stops growing, and added glucose, and found that the brain continued growing, producing chickens with bigger brains. The "genes" of a chicken, as part of a system, have something to do with the development of that system, but the environment existing in and around the organism is able to guide and support the way the system develops. The size, complexity, and intelligence of the brain represents a very large part of the "information" contained in the organism, and Zamenhof's experiment showed that the ability to realize this potential, to create this complexity, comes from the support of the environment, and that the "genetic nature of the chicken" didn't constitute a limit to the development of its brain.

I am going to argue that Alzheimer's disease is analogous to the situation confronted by the developing chicken embryo or the rat or human fetus, when the environment is unable to meet the needs of the highly energetic, demanding and sensitive brain cells, and the brain cells begin to die, instead of developing into a more complex state, passing beyond various barriers and limitations. There are two stereotypes that are in conflict with this view: (1) That the structure of the brain is determined at an early point in life, sometimes explicitly stated as the age of 12 or 16, and (2) that the structure of the brain goes into an "entropic" deterioration during the process of aging. My position is that the brain cells are in a vital developmental process at all times, and that the same things that injure the brain of a fetus also injure the brain of an aging person.

If novelty is really appearing during development, then it is hard to maintain that "entropy increases" during the development of an individual. Isn't a child a richer organization than a fertilized egg? Isn't an adult more individualized or realized than an infant? Seen from

the inside, our known world gets richer with experience. Learning is certainly anti-entropic. Where does the idea of "increasing entropy with living" come from? Many things contribute, including a doctrine of genetic determinism, the old Platonic idea of the imperfection of the concrete, the unreality of the existent, and the medieval idea of the "corruption of the body." These philosophies still motivate some people in aging research. The astrophysicist, N. A. Kozyrev, showed that the idea of an "entropic cosmos" derived simply from the assumptions of 19th century deism, "God set the clockwork universe in motion, and left it to run down." Early in this century, Raymond Pearl argued that the "rate of living" governed the life-span, so that "fast living" meant a short life. He based his argument on cantaloupe seeds: the faster they grew, the sooner they died. This was because he didn't give them anything but water, so they had to live on their stored energy; if they grew quickly, obviously they ran out of stored energy sooner. I have never heard that described as a stupid idea, but I think politeness is sometimes carried too far. In the clock analogy, or the seed analogy, the available energy is used up.

The clock with its wound-up spring and the seed in a dish of water may be considered as closed systems, and we can understand their fate. But if it is foolish to argue from a confined seed to free-living organisms, then it is just as foolish to argue from a clock to a cosmos. Unfortunately, these inferences about closed systems are often applied to real situations that aren't energetically closed.

The "rate of living" theory of aging picked up the idea of aging as a natural physical property of time, and gave it expression in mathematical form, arguing[3] that "the total lifetime entropy production" could be calculated, to give insight into "life expectancy and evolutional development." Unfortunately, the equation Hershey used assumed that the flow of heat out of the body into the surroundings is reversible. This suggests an image of Dr. Frankenstein vivifying his monster with lightning, putting the heat back into the body. If heat is to be "put back into the body," it is necessary to make sure that it is appropriate for the structure as it exists.

Actually, it is just the directed flow of energy which generates the structures. If any biological argument can be made from the idea of entropy, it is that it would be extremely difficult to regenerate food, by putting heat into a person. In a few situations, it is possible to show that living structures can directly absorb heat from their environment (caus-

ing the temperature to fall)—"negative heat production"—but the exact meaning of this isn't clear.[4] "It is now clear that in both crustacean…and mammalian[5] non-myelinated fibres there is an initial production of heat during (or soon after) the action potential, 80 % of which is rapidly reabsorbed."[6] A. I. Zotin,[7] citing the theory of Prigogine-Wiame, argued that the aging process involves both a decrease in entropy and a decrease in the rate of heat production.

Regeneration involves a production of entropy, as when an egg is formed. (The temperature fluctuation at the time of ovulation might make a contribution to the construction of the entropic egg.) The argument that aging of the animal (like aging of the cosmos) is governed by "the tendency of entropy to increase" has led people to say that rejuvenation would be like unscrambling an egg. Zotin's argument is interesting, because he says that an egg is a "scrambled animal." This view is very much like Warburg's and Szent-Györgyi's theory of cancer, that it is like a reversion to a simpler state of life. To sketch out what I have argued in different contexts, water is the part of the living substance that we can most meaningfully discuss in terms of entropy. In fact, much of the concept of entropy has derived from the study of water, as it changed state in steam engines, etc. Cancer cells, like egg cells, have a higher water content than the differentiated, functioning cells of an adult, and the water is less rigidly ordered by the cellular molecules. This different, more mobile state of the water, can be measured by the NMR (nuclear magnetic resonance) machines which are used for MRI (magnetic resonance imaging).

Estrogen has a special place in relation to the water in an organism. It is intimately involved with the formation of the egg cell, and wherever it operates, it increases both the quantity of water and, apparently, the disorder of the water. Its function, I believe, is to promote regeneration, as in Zotin's scheme, by increasing entropy, or "scrambling the animal." The way it promotes regeneration is by promoting water uptake, stimulating cell division, and erasing the differentiated state to one degree or another, providing a new supply of "stem cells," or cells at the beginning of a certain sequence of differentiation. These more numerous cells then must find a hospitable environment in which to develop and adapt. If the proper support can't be found, then they will be recycled, like the unfed cells in the brain of a fetus. If we imagine the course of development as a summary of evolution ("ontogeny recapitulating phylogeny"), then

the egg, as it "unscrambles" itself in embryonic development, passing through stages resembling jelly fish, worm, fish, reptile, bird, baboon, keeps finding that the available energy allows it to, in effect, say "I want this, I don't want that," until it emerges as a human baby, saying "I want," and begins eating and learning, and with luck continues the unscrambling, or self-actualization. Degenerative aging, rather than being "physically derived from the properties of time," seems to be produced situationally, by various types of contamination of our energy supply. Unsaturated fats, interacting with an excess of iron and a deficiency of oxygen or usable energy, redirect our developmental path.

The saturated fats, in themselves, seem to have no "signalling" functions, and when they are naturally modified by our desaturating enzymes, the substances produced behave very differently from the plant-derived "eicosanoids." As far as their effects have been observed, it seems that they are adaptive, rather than dysadaptive. All of the factors that affect the brain of a fetus should be examined in relation to the aging brain. Besides estrogen and fats, I am thinking of oxygen and carbon dioxide, glucose, iron and calcium, cholesterol, progesterone, pregnenolone, DHEA, the endorphins, GABA, thyroid, and vitamin A. An additional factor, endotoxin poisoning, eventually tends to intervene during stress and aging, exacerbating the trend begun under the influence of the other factors.

IV. False Signals from the Environment

The environment can be supportive, but it can also divert development from an optimal course.

Passively taking whatever you are given, by history and nature, is entropic; choosing intelligently from possible diets, selecting courses of action, will create pattern and reduce entropy. If education contains an element of choice and self-actualization, then the results seen in several Alzheimer's studies could have a significance larger than what has been suggested by the investigators. A diagnostic bias has been reported to result from the use of standardized tests based on vocabulary, because education increases vocabulary, and tends to cover up the loss of vocabulary that occurs in dementia. In the Framingham study, it was concluded that there was a real association of lower educational

level with dementia, but the suggestion was made that self-destructive practices such as smoking were more common among the less educated.

The Seattle study of the patients in a health maintenance organization showed a very distinct difference in educational level between the demented and the non-demented, both of whom had roughly similar frequency of prescriptions for estrogen. The features that seemed important to me, that weren't discussed by the authors, were that the demented women had a much lower rate of progestogen use, and a much higher incidence of hysterectomy, which interferes with natural progesterone production. Although Brenner, et al., in the Seattle study concluded that "this study provides no evidence that estrogen replacement therapy has an effect on the risk of Alzheimer's disease in postmenopausal women," they reported that "Current estrogen use of both the oral and the vaginal routes had odds ratios below 1, while former use of both types yielded odds ratios above 1…" (They seem to neglect the fact that Alzheimer's-type disease in old people has a long developmental history, so it is precisely the "former" use that is relevent. 31 % of the demented women had formerly used estrogen, and only 20 % of the control group. Since estrogen is a brain excitant, present use creates exactly the same sort of effect on verbal fluency and other signs of awareness of the environment that a little cocaine does. Anyone who neglects this effect is probably deliberately constructing a propaganda study.)

This observation, that the demented had 155 % as much former estrogen use as the normal group, as well as the difference in rates of progestogen use (normal patients had 50 % more progestogen use than demented) and hysterectomy (demented had 44.1 % vs. 17 % in the normals, i.e., 259 % as many; the incidence of hysterectomies after the age of 55, which is a strong indication of a natural excess of estrogen, in the demented was 374 % of the incidence in the non-demented), should call for a larger study to clarify these observatons, which tend to indicate that exposure to estrogen in middle-age increases the risk of Alzheimer's disease in old age, and that even medical progestogens offer some protection against it.

(Although this study might have been bigger and better, it is far better than the junk-studies that have been promoted by the pharmaceutical publicity machine. I have seen or heard roughly 100 mentions of the pro-estrogen anti-scientific "studies," and none mentioning this one.)[8]

"Women tend to have higher age-specific prevalence and incidence rates of Alzheimer's disease than do men."[9,10]

"Commonly used dementia screening tests may be unfair to poorly educated individuals, especially women and rural residents."[11]

Signals in the Abstract

When I taught endocrinology, I annoyed my tidy-minded students by urging them to consider the potential hormone-like action of everything in the body, and to think of layers of control, ranging from sugar, salt, and carbon dioxide, through the "official hormones," to complex nervous system actions such as expectancy, and biorhythms. Certain things that are active in very important processes deserve special attention as "signals," but they still have to be understood in context. In this sense, we can think of Ca_2^+ as a signal substance, in its many contexts; it is strongly regulated by the cell's energy charge. Magnesium and sodium antagonize it in certain situations. Linoleic acid, linolenic acid, arachidonic acid: Their toxicity is potentially prevented by the Mead acids, and their eicosanoid derivatives, which behave very differently from the familiar prostaglandins, as far as they have been compared; can be drastically reduced by dietary changes. Prostaglandins, prostacyclin, thromboxane: Formation is blocked by aspirin and other antiinflammatory drugs.

- Adenosine: Sleep inducing protective effect. Adenosine is structurally very similar to inosine, another natural substance (found in meat, for example) which is a component of "inosiplex," an antiviral drug[12,13] or immunostimulant which has also been found to have an anti-senility effect.[14] Adenosine is a free radical scavenger, and protects against calcium and glutamate excitotoxicity.[15,16] It also appears to protect against the relative hyperventilation that wastes carbon dioxide, and endotoxin can interfere with its protective action. Guanosine, in this same group of substances, might have some similar properties. Thymidine and cytidine, which are pyrimidine-based, are endogenous analogs of the barbiturates, and like them, they might be regulators of the cytochrome P_{450} enzymes. Uridine, in this group, promotes glycogen synthesis, and is released from bacteria in the presence of penicillin.
- Iron: Regulator of mRNA stability, heme synthesis; reacts with reductants and unsaturated oils, to produce free radicals and lipid

peroxides; its absorption is increased by estrogen, hypothyroidism, anemia or lack of oxygen. Glutamate and aspartate, excitotoxins, and GABA, an inhibitory transmitter.

- These have metabolic links with each other, with ammonia, and with stress and energy metabolism.
- Estrogen and acetylcholine, excitotoxins.[17] The information on this is overwhelmingly clear, and the publicity to the contrary is a horrifying example of the corruption of the mass media by the drug industry.
- Endorphins: Stress induced, laterally specific, involved in estrogen action, antagonized by naloxone and similar anti-opiate drugs. I have proposed that the endorphins can cause or sustain some of the symptoms of aging. Naloxone appears to be a useful treatment for senility.[18,19]
- Endotoxin: Antimitochondrial action, causes elevation of estrogen. It synergizes with unsaturated fats, and naloxone opposes some of its toxic effects.
- Urea, cholesterol: Structural stability of proteins and lipid-protein complexes.
- Things that act directly on the water structure: I think all of the natural regulators have an effect on the structure of water, but some unusual substances seem to act primarily on the water. Noble gases, for example, have no chemical effects, but they tend to form "cages" of water molecules around themselves. Camphor, adamantane, and the antiviral drug amantadine, probably have a similar water-structuring effect, and amantadine, which is widely used as a therapy in Parkinson's disease, has an anti-excitotoxic action.

V. Hormone Imbalance, Leading to Failure of Protective Inhibition and Alzheimer's Disease

"All cell death is characterized by an increase of intracellular calcium…" "Increase of cytoplasmic free calcium may therefore be called 'the final common path' of cell disease and cell death. Aging as a background of diseases is also characterized by an increase of intracellular calcium. Diseases typically associated with aging include hypertension, arteriosclerosis, diabetes mellitus and dementia."[20]

The Function of Energy

Most people are slightly demented now and then, when they are very sleepy or tired, or sick, or drunk, or having a hormone imbalance or extreme anxiety state. Sometimes physicians have described people as demented, implying that the condition would never improve, when the person was depressed or hypothyroid. If the person has a history of epilepsy, or is very old, the physician is more likely to diagnose dementia than if the same loss of mental function occurs in a younger person without a history of a nervous disorder. Even people with less education are at increased risk of being diagnosed as "demented."

In 1976, I saw a 52 year-old woman who had the diagnosis of epileptic dementia. After 3 or 4 days of taking progesterone, her mental function returned to the extent that she could find her way around town by herself, and could work. A few months later, she returned to graduate school, got straight As and a master's degree. A few years later, a man in his 80s showed the classical signs of senile dementia, with childishness, confusion, self-centeredness, and unstable emotions. A few days after getting a mixture of thyroid, pregnenolone, and progesterone, his mind was again clear, and he was able to work on a research project he had set aside years before.

When the body temperature is very much below normal, mental functioning is seriously limited. I think the first question that should be asked about a demented person is "is this the cold brain syndrome, or is something else involved?" When it is known that the brain has shrunken drastically, and filled up with plaques and developed gliosis, we know that something more than a "cold brain" is involved, but we don't know how much function could be regained if the hormones were normalized. Every moment of malfunction probably leaves its structural mark. Early or late, it is good to prevent the functional errors that lead to further damage, and to give the regenerative systems an opportunity to work. Before the final "calcium death" described (above) by Fujita, there are many opportunities for intervening to stop or reverse the process. The older the person is, the more emphasis should be put on protective inhibition, rather than immediately increasing energy production. Magnesium, carbon dioxide, sleep, red light, and naloxone might be appropriate at the beginning of therapy.

The resting state of a cell is a highly energized state. To the old Pavlovians, the resting state existed at two energy levels, and they applied the term "protective inhibition" generally to the depleted state (parabiosis) that occurs in exhaustion or coma, but I am using the phrase in a more general sense, that seems reasonable now that the concept of "excitotoxic" injury has become current. I mean it to include everything which protects against excitotoxic injury. This definition therefore has the virtue of being biochemically and physiologically very specific, while retaining the functional and therapeutic significance that it had for the Pavlovians. (My book, *Mind and Tissue*, and the chapter "A Unifying Principle" in *Generative Energy*, discussed the idea of the resting state and protective inhibition.)

Ordinary healthy sleep is an example of restorative, protective inhibition. The energy charge, including levels of ATP, creatine phosphate, and glycogen storage, regulates many restorative enzyme systems. I have suggested[21] how the entropy-sensitivity or cold-inactivation of an enzyme could be involved in shifting the brain toward a state of inhibition. A recent publication[22] has proposed that reduction of energy charge and depolarization of cells act through adenosine secretion to restore glycogen stores. Since glycogen stores decrease with aging, this work supports the idea that protective inhibition is weakened with aging.[23]

"…The conditions that have been demonstrated to stimulate adenosine release from neural tissue represent either increases in metabolic demand (…activation of excitatory receptors) or decreases in metabolic supply (hypoxia, ischaemia, hypoglycemia)…" "In the brain, adenosine-stimulated increases in potassium conductance produce hyperpolarization, thereby reducing neuronal responsiveness…" "Adenosine release is triggered globally in response to changes in cerebral energy homeostasis." "A number of findings provide indirect support for the hypothesis that glycogen stores are depleted during waking and restored during sleep." "Reduced availability of glycogen to astrocytes must…increase adenosine release…" "Because ATP concentration is 100-fold greater than AMP concentration, a minute decrease in cellular energy charge…is translated into a large proportional increase in extracellular adenosine cencentration…"[22]

The terms "functional quiescence" and "G_0 quiescence" are similar in meaning to the resting state; I think of cells in the state of "G_0 quiescence" as being stem cells, waiting for use in regeneration, but I don't

subscribe to the idea that they can't be reconstituted from functioning, differentiated cells. In plants, dedifferentiation is achieved fairly easily, and in the study of animal cells the trend in that direction seems very obvious, though many people keep saying that it just isn't possible. In general, the things such as lipid peroxidation or calcium influx which cause cell replication at one level, cause cell death at a higher level.

Energy to resist stress makes quiescence possible, and prevents the deterioration of cells, of the sort that occurs in aging.[24] "Experiments performed with endothelial cells in the context of the ischemia-reperfusion toxicity of free radicals, also offer good examples of the impact of cell energy on cell resistance to these toxic molecules." "…If a supplement of energy is given…the toxic effect of the free radicals is much reduced…"

The specific approaches of this orientation—to energize but quiet the brain—are diametrically opposed to some of the "therapies" for Alzheimer's disease that have been promoted recently by the drug industries: Things to increase stimulation, especially to increase cholinergic excitation; even the excitotoxic amino acids themselves and their analogs; and estrogen, which is a multiple brain excitant, proconvulsant, excitotoxic promoter, and anti-memory agent. Those product-centered publications stand out distinctly from the actual research.

There are many energy-related vicious circles associated with aging, but the central one seems to be the fat-thyroid-estrogen-free-radical-calcium sequence, in which the ability to produce stabilizing substances including carbon dioxide and progesterone is progressively lost, increasing susceptibility to the unstable unsaturated fats.

Effects of Estrogen and Unsaturated Fatty Acids

Estrogen production is facilitated when tissue is cooler, and it lowers body temperature. Estrogen and the endorphins act together in many ways (including the behavior of estrus), and naloxone (the antagonist of morphine and the endorphins) raises body temperature and in other ways opposes estrogen. Naloxone has been found to improve the symptoms of demented people, and I have seen it quickly, and dramatically, improve the mental clarity of a 60 year old woman who had used estrogen. It, like clonidine (the anti-adrenaline drug), is a good candidate for controlling the hot flashes and other symptoms of menopause.

In various degenerative brain conditions, blood clotting has been implicated either as a cause or a complication. Many people are promoting unsaturated oils for their "anti-clotting" value, in spite of the older literature showing that they inhibit proteolytic enzymes and slow clot removal. Several newer publications have revealed other aspects of their involvement in thrombus formation. Corn oil caused platelets to be more sensitive to ADP.[25]

Although there is a lot of talk about "membrane fluidity," as a desirable thing, and the loss of unsaturated lipids in the aged brain, there are some interesting observations related to "viscosity" in Alzheimer's disease. The platelets of Alzheimer's patients are less viscous, and lipids extracted from the brain are more fluid, and contain 30 % less cholesterol than normal (on a molar basis, in relation to phospholipids).[26] In general, lipid peroxidation causes cellular viscosity to increase, apparently by causing cross-linking of proteins, but I think the significance of the decreased cholesterol relates to its significance as precursor to pregnenolone and progesterone, and to the known association with Alzheimer's disease of a variant form of the cholesterol transporter protein, ApoE, which I suppose is a slightly less stable molecular form that is more susceptible to malfunction in stress.

The extracellular matrix is a major factor in the function and stability of brain cells.[27] (Any factor producing edema tends to disrupt the extracellular matrix.[28–30])

Seizures are known to be promoted by estrogen, by unsaturated fats, and by lipid peroxidation, and to cause an increase in the size of the free fatty acid pool in the brain. Prolonged seizures cause nerve damage in certain areas, especially the hippocampus, thalamus, and neocortex.[31] Dementia is known to be produced by prolonged seizures.

Prenatal exposure to estrogen, to oxygen deficiency, or to unsaturated fats decreases the size of the brain at birth. There is apparently a requirement for saturated fats during development.[32]

Under the influence of estrogen, or unsaturated fats, brain cells swell, and their shape and interactions are altered. Memory is impaired by an excess of estrogen. Estrogen and unsaturated fat and excess iron kill cells by lipid peroxidation, and this process is promoted by oxygen deficiency. The fetus and the very old have high levels of iron in the cells. Estrogen increases iron uptake. Estrogen treatment produces elevation of free fatty acids in the blood, and lipid peroxidation in tissues. This tends to

accelerate the accumulation of lipofuscin, age-pigment. Lactic acid, the production of which is promoted by estrogen, lowers the availability of carbon dioxide, leading to impairment of blood supply to the brain.

Estrogen stimulates cell division, but can also increase the rate of cell death. Unsaturated fatty acids can also stimulate or kill.

Both estrogen and unsaturated fats promote the formation of age-pigment. Besides increasing the free fatty acid concentration, estrogen possibly depresses the level of cholesterol, both of which are changes seen in the senile brain.

Estrogen causes massive alterations of extracellular matrix, and seems to promote dissolution of microtubules (Nemetschek-Gannsler), as calcium does. Unsaturated fats increase calcium uptake by at least some brain cells.[33] Unsaturated fats, like estrogen, increase the permeability of blood vessels. The unsaturated fat causes edema of the brain, inhibits choline uptake, blocking acetylcholine production.

Progesterone is a nerve growth factor, produced by glial cells (oligodendrocytes). It promotes the production of myelin, protects against seizures, and protects cells against free radicals. It protects before conception, during gestation, during growth and puberty, and during aging. It promotes regeneration. Its production is blocked by stress, lipid peroxidation, and an excess of estrogen and iron.

Aspirin protects against iron toxicity, clot formation, and reduces lipid peroxidation while blocking prostaglandin formation. Aspirin and other antiinflammatory drugs, taken for arthritis, have been clearly associated with a reduced incidence of Alzheimer's disease. Aspirin reduces the formation of prostaglandins from arachidonic acid.

Unsaturated fatty acids, but not saturated fatty acids, are signals which activate cell systems.

Many different stimuli can induce cell activity, cell death, or change to another cell type. ("…Hippocampal astrocytes from kainate-treated rats experess A_2B_5 immunoreactivity, a marker of type-2 astrocytes." "This suggests that in the CNS, normal resident astrocytes acquire the phenotypic properties of type-2 astrocytes."[34])

A "deficiency" of polyunsaturated fatty acids leads to altered rates of cellular regeneration and differentiation, a larger brain at birth, improved function of the immune system, decreased inflammation, decreased mortality from endotoxin poisoining, lower susceptibility to lipid peroxidation, increased basal metabolic rate and respiration, increased thyroid

function, later puberty and decreases other signs of estrogen dominance. When dietary PUFA are not available, the body produces a small amount of unsaturated fatty acid (Mead acids), but these do not activate cell systems in the same way that plant-derived PUFAs do, and they are the precursors for an entirely different group of prostaglandins.

Vitamin A and the Steroids

In a variety of cell types, vitamin A functions as an estrogen antagonist, inhibiting cell division and promoting or maintaining the functioning state. It promotes protein synthesis, regulates lysosomes, and protects against lipid peroxidation. Just as stress and estrogen-toxicity resemble aging, so does a vitamin A deficiency. While its known functions are varied, I think the largest use of vitamin A is for the production of pregnenolone, progesterone, and the other youth-associated steroids. One of vitamin E's important functions is protecting vitamin A from destructive oxidation. Although little attention has been given to the effects of unsaturated fats on vitamin A, their destruction of vitamin E will necessarily lead to the destruction of vitamin A. The increased lipid peroxidation of old age represents a vicious circle, in which the loss of the antioxidants and vitamin A leads to their further destruction.

To produce pregnenolone, thyroid, vitamin A, and cholesterol have to be delivered to the mitochondria in the right proportion and sufficient quantity. Normally, stress is balanced by increased synthesis of pregnenolone, which improves the ability to cope with stress. Lipid peroxidation, resulting from the accumulation of unsaturated fatty acids, iron, and energy deficiency, damages the mitochondrias' ability to produce pregnenolone. When pregnenolone is inadequate, cortisol is overproduced. When progesterone is deficient, estrogen's effect is largely unopposed. When both thyroid and progesterone are deficient, even fat cells synthesize estrogen.

The Nature of Alzheimer's Disease

Although Alzheimer's disease until recently referred to a certain type of organic dementia occuring in people in their thirties, forties and fifties (presenile dementia), structural similarities seen in senile dementia have caused the term to lose its original meaning. Alzheimer's sclerosis of blood vessels, and even the death of nerve cells, are sometimes neglected

in favor of the more stylish ideas, emphasizing certain proteins that cause the tangles and plaques. Until recently, the "tangles" were commonly interpreted as the debris left after the death of a cell, rather than as one of the processes causing the death of the cell.

Alzheimer-type dementia is different from other dementias, but it overlaps with them, and with age-related and stress-related changes in other organs.

Physical signs (seen at autopsy) of AD:

1) Death of neurons (increase of glial cells),

2) Amyloid plaques (extracellular), associated with a particular variant of apolipoprotein E, the epsilon 4 allele,

3) Fibrillary tangles (intracellular, or remaining after the rest of the cell has disappeared),

4) Amyloid in blood vessels.

Functional and biochemical observations:

1) The mitochondrial energy problem, cytochrome oxidase and its regulation; body temperature/pulse-rate cycle disturbance; lipid peroxidation; respiratory defect; altered amino acid uptake; memory impairment; dominance of the excitatory systems vs. the inhibitory adenosine/GABA/progesterone/pregnenolone system. Increased calcium uptake, which is associated with lipid peroxidation and cell death. Increased cortisol and DHEA.

2) Deposit of abnormal proteins, such as transthyretin-amyloid; albumin binding of PUFA, vs. transport of thyroid and retinol. Beta-glucuronidase increases, depositing estrogen in cells.[35]

3) Abnormally phosphorylated (tau) proteins; association with the variant form of Apo E; tau microtubule organizing proteins, microtubules are involved in transporting cholesterol; phosphorylation, by the kinase systems, regulated by PUFA; the intermediate filaments are generally stress-associated.

4) ApoE, in cytoplasm, involved in cholesterol delivery for pregnenolone synthesis, as in the adrenal; its expression regulated by thyroid. Regulation of the side-chain cleaving enzymes; regulation of the cholesterol intake and conversion to pregnenolone by the endozepine receptor/GABA receptor, modified by progesterone.

An Example of a Regulatory Problem

Vegetable oil suppresses the thyroid, increasing estrogen. Estrogen and calcium depolymerize microtubules. Microtubule transport for Apo E, transthyretin, thyroid, and cholesterol for pregnenolone synthesis is disrupted. Transthyretin and Apo E accumulate unused, and deposit in blood vessels, around nerves, and in cytoplasm. Pregnenolone and progesterone deficiency (aggravating thyroid deficiency) causes memory loss, destabilization of nerve cells, failure of myelin formation, and excess cortisol synthesis. Free radicals and calcium cause multiple cell injuries including nerve-death. Estrogen is released by elevated beta-glucuronidase. Imbalances of other steroids, including cortisol and DHEA, develop as cells compensate for pregnenolone deficiency, causing shifts in balance of glial cells. Hypothyroidism, estrogen excess, free unsaturated fats cause increased vascular permeability and brain edema, protein leakage, and alteration of the matrix.

VII. Structure as a Regulatory System---An Emerging Vision of Pervasive Epigenesis

In the introduction I mentioned that membranous regulation and genetic determination should be considered as defunct theories. What I have been saying about self-actualizing systems and the factors that disrupt them derives from a view of cell function that has been developing since the 1920s.

Around 1940, a Russian biochemist (Oparin, I think) proposed that the enzymes of glycolysis were bound to the structure of the cell when they were not in use, and that they were "desorbed" under the conditions that required abundant glycolysis. Knowing that concept, in 1970 I proposed that the cell water itself underwent a transition under such conditions (which could include increased temperature, reduced oxygen, or nervous or hormonal stimulation). Activation of glycolysis is usually

explained by the availability of regulatory substances such as ammonia, phosphate, and NAD, and many biochemists were content to understand cells in terms of test-tube models. But in the last few years, it has become clear that some of these basic regulatory molecules do bind to structural components of the cell.[36] Although the details aren't clear, it is known that hormones and other factors stabilize or destabilize RNA, and that during some of these events relevant enzymes bind to the RNA. When these facts are combined with the information that is accumulating on splicing and modification of RNA, and the copying of RNA back into DNA, the hereditary system is seen to be much more flexible than it was believed to be.

A global change of state is able to steer each part of the process, continuously. In this way, the cell resembles an analog, rather than a digital, control system: each part is momentarily guided, rather than waiting for "feedback."

Where before, cellular "regulatory mechanisms" referred to certain feedback mechanisms based on interactions of randomly diffusing molecules, the new understanding of the cell sees a highly structured system in which very little is random, and the cell's adaptive possibilities, instead of being limited to a certain number of genetic switches, are shaped by every imaginable environmental influence. The cell's structure, far from being "read out of the genome," is sensitively reshaped constantly by processes that incorporate some of the environment in establishing each new stability. The old-model-geneticists have been forced to admit that the genes can't specify everything in the organism's structure, and it was the brain's complexity that forced this recognition that certain things are developed "epigenetically." But the new fact that most biologists are reluctant to accept is that the structure of the cell itself is developed very largely on the basis of information received from the environment—that is, "epigenetically."

Traditionally, epigenesis has meant that the form of an embryo or organism didn't preexist, or wasn't completely specified by the genes. That is, it has had to do with the relationships between cells. It involved a recognition that "cells are clever enough to design an organism." It is a significant step beyond that to the recognition that "cells are clever enough to redesign themselves to meet situations never seen before."

Biologists working with bacteria and yeasts have seen them adapt in non-random ways to novel conditions. "Directed mutations" are

impossible, according to the "central dogma" that has the support of textbooks and most biology professors, but they do occur in those single-celled organisms. Barbara McClintock showed that in corn her mobile genes were mobilized by stress. Although this isn't exactly "directed mutation," it is an example of a mechanism for increasing adaptation when adaptation is need. There is a certain type of enzyme which makes specific cuts in the DNA chain. Biotechnologists find them convenient for their purposes, but their presence serves physiological purposes, presumably in all organisms, like those described by McClintock in corn. During the terminal stress that produces the special kind of cell death known as apoptosis, these enzymes make confetti of the genome.

Poisons, such as estrogen, unsaturated fatty acids, or even radiation, produce different effects at different doses. Low doses typically stimulate cell division, larger doses produce changes of cell type and altered states of differentiation, and finally, adequate doses produce apoptotic cell death. There is a special ideology around apoptosis, which holds that it is "genetically programmed," implying that whenever it occurs in the brain, it was destined to happen sooner or later. But in fact, "growth factors" of various sorts can prevent it. It is increasingly clear that it represents excessive stress and deficient resources. The involvement of the genetic apparatus in differentiation and radical adaptation suggests that the (epigenetic) resources of cells are unlimited.

The changes that are known to be produced by the poisons that we are habitually exposed to are exactly the changes that occur in the aging brain. As I scan over hundreds of studies that define the effects of estrogen, unsaturated fats, excess iron, and lipid peroxidation, my argument seems commonplace, even trivial, except that I know that it clearly relates to therapies for most of the degenerative diseases, and that the great culture-machine is propagating a different view at several points that are essential for my argument.

They are advancing a myth about human nature, so I will advance a counter-myth. At the time people were growing their large brains they lived in the tropics. I suggest that in this time before the development of grain-based agriculture, they ate a diet that was relatively free of unsaturated fats and low in iron—based on tropical fruits. I suggest that the Boskop skull from Mt. Kilimanjaro was representative of people under those conditions, and that just by our present knowledge of the association of brain size with longevity, they—as various "Golden Age"

myths claim—must have had a very long life-span. As people moved north and developed new ways of living, their consumption of unsaturated fats increased, their brain size decreased, and they aged rapidly. Neanderthal relics show that flaxseed was a staple of their diet.

Even living in the tropics, there are many possibilities for diets rich in signal-disrupting substances, including iron, and in high latitudes there are opportunities for reducing our exposure to them. As a source of protein, milk is uniquely low in its iron content. Potatoes, because of the high quality of their protein, are probably relatively free of toxic signal-substances. Many tropical fruits, besides having relatively saturated fats, are also low in iron, and often contain important quantities of amino acids and proteins. In this context, Jeanne Calment's life-long, daily consumption of chocolate comes to mind: As she approaches her 121st birthday, she is still eating chocolate, though she has stopped smoking and drinking wine. The saturated fats in chocolate have been found to block the toxicity of oils rich in linoleic acid, and its odd proteins seem to have an anabolic action.

If we really take seriously even the traditional sort of epigenesis, and especially if we accept the deeper idea of epigenesis on the level of cellular structure and function, we have to see the organism as a sort of "whirlwind of cells," made up of whirlwinds of atoms (in Vernadsky's phrase) in which our way of life sets the boundaries within which our cells will restructure themselves.

The random production of free radicals, rather than acting only by way of genetic damage or protein cross-linking, is also able to act as a signalling process, that is, on a strictly physiological level. An excess of unsaturated fatty acids itself constitutes a massive distortion of the regulatory systems, but it also leads to distortions in the "eicosanoid" system and the increasingly uncontrolled production of free radicals, and to changes in energy, thyroid activity, and steroid balance. The aging body, rather than being like a car that needs more and more repairs until it collapses from simple wear, is more like a car traveling a road that becomes increasingly rough and muddy, until the road becomes an impassable swamp.

The suggested therapy is a correction of the signalling process, rather than "genetic surgery," transplantation, etc., which is the pessimistic implication of the doctrine that oxidative damage is simply a matter of "wear and tear," "somatic mutations," and "cross-linking." Those

problems are reparable, and our emphasis should be on the production of energy and the avoidance of the conditions that allow the undesirable signals to accumulate.

The absence of cancer on a diet lacking unsaturated fats, the increased rate of metabolism, decreased free radical production, resistance to stress and poisoning by iron, alcohol, endotoxin, alloxan and streptozotocin, etc., improvement of brain structure and function, decreased susceptibility to blood clots, and lack of obesity and age pigment on a diet using coconut oil rather than unsaturated fats, indicates that something very simple can be done to reduce the suffering from the major degenerative diseases, and that it is very likely acting by reducing the aging process itself at its physiological core.

The Progesterone Deceptions

Ray Peat's Newsletter, 2007

In the 1930s, it was demonstrated that estrogen, even in small doses, produced abortions, and that when it is given early enough, even a very small dose will prevent implantation of the fertilized embryo. Progesterone was known, by the early 1940s, to protect against the many toxic effects of estrogen, including abortion, but it was also known as nature's contraceptive, since it can prevent pregnancy without harmful side-effects, by different mechanisms, including prevention of sperm entry into the uterus. That is, progesterone prevents the miscarriages which result from excess estrogen,[1,2] but if used before intercourse, it prevents conception, and thus is a true contraceptive, while estrogen is an abortifacient, not a contraceptive.

In the 1950s, there was a search for chemicals which would prevent ovulation. According to Carl Djerassi, drug companies were extremely reluctant to risk a religious backlash against their other products, and so hesitated to market contraceptives. Obviously, the induction of monthly abortions would have been even harder to sell.

According to Djerassi,[3] "Until the middle 1940s it was assumed that progesterone's biological activity was extremely specific and that almost any alteration of the molecule would diminish or abolish its activity." This would obviously discourage interest from the drug companies, who could patent a substance which they had chemically modified, but could not patent a simple natural substance. However, many substances—even non-steroidal chemicals—were known to have estrogenic action.[4]

By 1942, Hans Selye had demonstrated that natural steroids retain their activity when administered orally. But every drug company with a steroid patent had an obvious interest in having the public believe that there is a reason that the natural steroids cannot be conveniently used. The doctrine that natural steroids are destroyed by stomach acid appeared, was promoted, and was accepted—without any supporting evidence. In the manufacture of progesterone, the precursor steroid is boiled in hydrochloric acid to free it from its glucose residue. No one seriously believed that stomach acid hurts progesterone, except the public—and the doctors, who had seen the claim in their medical journals, and had heard it from drug salesmen.

The myth stopped the use of the cheap tablets of progesterone, as tablets of the synthetic "progestins" came on the market, at a much higher price. Doctors who insisted on using real progesterone were forced to buy it in an injectable form. As a result, solubility became an issue. Progesterone is extremely insoluble in water, and, though it is vastly more soluble in vegetable oil than in water, it does not stay in solution at room temperature even at the low concentration of 1 part in 1000 parts of a typical vegetable oil.

When people speak of an allergy to progesterone (or even to penicillin) they generally are not aware of the presence of a very toxic solvent.[5] For a time, progesterone was often sold dissolved in benzyl benzoate. The Physician's Desk Reference warned of possible allergic reactions to progesterone. Now, it is supposedly sold dissolved in vegetable oil, with about 10 % benzyl alcohol as—supposedly—a "bacteriostatic agent."

Bacteriostatic water contains 0.9 % to 1.9 % benzyl alcohol, and can irreversibly harm nerves.[6,7] Its use in hospitals killed thousands of babies. Awareness of benzyl alcohol's toxicity goes back to 1918 at least; it was proposed as an effective insecticide, and was found to be toxic to many animal systems. The safe systemic dose[7] is exceeded with an injection of 150 mg. of progesterone, yet the local concentration is far higher. It can cause a severe reaction even when used at a lower concentration, in bacteriostatic water.[5]

Other alcohols, including ethanol, have been used as solvents, but since they (ethanol even more than benzyl alcohol) have an affinity for water, the solution decomposes in contact with tissue water.

In spite of the toxicity of the vehicle, several beneficial effects can be obtained with injected progesterone, in serious conditions such as epilepsy or cancer of the breast or uterus. Many researchers have commented on the very obvious difficulty of giving very large amounts of progesterone.[8] My comparisons of oral progesterone in tocopherol with other forms and methods of administration show a roughly similar efficiency for oral and inject progesterone, and about 1/20 the effect for suppositories. Crystals of progesterone are visible in the suppositories I have examined, and this material is obviously wasted.

An old theory of vitamin E's mechanism of action in improving fertility was that it spares progesterone.[9] It is established that some of the effects of vitamin E and progesterone are similar, for example, both

prevent oxygen waste and appear to improve mitochondrial coupling of phosphorylation with respiration. I suspected that if they actually both work at the same mitochondrial site, then they must have a high mutual solubility.

Knowing the long-standing problem of administering large doses of progesterone without a toxic solvent, I applied for and was granted a patent for the composition of progesterone in tocopherol. One of my reasons for publishing in the form of patents is that I have had many years of experience in having my discoveries taken up by others without acknowledgment, if they are compatible with conventional prejudices. Typically, an editor rejects a paper, and then a few months later publishes a very similar paper by someone else. My dissertation research, which established that an estrogen excess kills the embryo by suffocation, and that progesterone protects the embryo by promoting the delivery of both oxygen and glucose, didn't strike a responsive chord in the journals which are heavily influenced by funds from the drug industry.

According to a consultant for a major medical journal, the idea "…of dissolving progesterone, a fat soluble steroid hormone, in vitamin E which is then incorporated into chylomicrons absorbed via the lymphatics, and thus avoids the liver on the so called first pass…is so simple it is amazing that the pharmaceutical companies have not jumped on it." (A more sophisticated writer might have said "…stomped on it.")

In the powder form, direct and intimate contact with a mucous membrane allows lipid phase to lipid phase transfer of progesterone molecules. Instead of by-passing the liver, much of the progesterone is picked up in the portal circulation, where a major part of it is glucuronidated, and made water soluble for prompt excretion.

Since this glucuronide form cross-reacts to some extent with the ordinary progesterone in the assay process, and since 50 % of the ordinary free progesterone is carried inside the red blood cells,[10,11] and 50 % is associated with proteins in the plasma, while the glucuronide hardly enters the red blood cells at all, it is better to judge by clinical efficacy when comparing different oral forms. My comparisons show several times higher potency in the tocopherol composition than in powder form.

Since progesterone's use as a drug antedates the 1938 law requiring special federal approval, its legal status is similar to that of thyroid

hormone. Unfortunately, for both thyroid and progesterone, there is a tendency to cut corners for the sake of a bigger profit margin.

For example, steroid acetates are generally a little cheaper than the simple natural steroid. Some people assume that an acetate or butyrate can be substituted for the steroid itself. This can cause dangerous reactions.

Medroxyprogesterone acetate is considered a progestin (though it is not supportive of gestation), because it modifies the uterus in approximately the way progesterone does, but it is luteolytic, and lowers the ovaries' production of progesterone while progesterone itself has a positive effect on the corpus luteum, stimulating progesterone synthesis. Defining "progestin" in a narrow way allows many synthetics to be sold as progestogens, though some of them are strongly estrogenic, allowing them to function as contraceptives—it is odd that contraceptives and agents which suppress progesterone synthesis should be officially called "supported of pregnancy." It is probably partly the acetate group in the medroxyprogesterone acetate molecule which makes it bind firmly to receptors, yet causes it to block the enzymes which would normally be involved in progesterone metabolism. (I think testosterone, even, might be a safer progestin than medroxyprogesterone acetate.) Pregnenolone acetate similarly blocks the enzymes which normally metabolize pregnenolone.[12] In aspirin, it has been found that it is the acetyl group which (by a free radical action) blocks an enzyme involved in prostaglandin synthesis.

If the category called "progestogens" or "progestins" is to be defined on the basis of a single tissue reaction, then it is possible to classify progesterone with the toxic synthetic substances, but then it becomes highly deceptive to imply that progesterone is just a progestin, or that it has any of the other properties of the toxic synthetics, but this continues to be done. The warnings about "progestins causing birth defects," for example, cause epileptic women to use conventional anti-seizure drugs (all of which cause birth defects) during pregnancy, and to avoid natural progesterone, which generally could control their seizures. Thus, a false message attached to progesterone creates precisely the harm it claims to want to prevent. In my communications with the regulatory agencies, I have concluded that their attempts to deceive are too blatant to ascribe to incompetence. Whether it's the Forest Service the FDA, the principle is

the same: The regulatory agencies have been captured by the regulated industries.

Another place to cut costs is in the tocopherol. Tocopherol acetate does have vitamin E activity, but since it is only about half as efficiently absorbed as the simple tocopherol,[13] it is a mistake to save a few dollars an ounce, at the expense of losing half of the therapeutic effect. People who have compared natural progesterone in natural tocopherols with other compositions have insisted that the other compositions must not contain progesterone.

The taste of natural vitamin E is stronger than that of the synthetic forms, but since the mixture is absorbed by any tissue it contacts, including various parts of the bowel, it can be taken in a capsule. If a small amount of olive oil is used with it, absorption through the skin is very rapid. Many women use it vaginally, spread onto a diaphragm, to hold it in contact with the membranes. The efficiency of absorption by all routes is so high that patients should be warned against its anesthetic effect, until their dosage requirement is known approximately. Some physicians prefer concentrations higher than 10 %, but the risk of accidental drunkenness or anesthesia is higher with the stronger solutions.

It is an indication of the tocopherol solution's high availability that medical researchers such as Roy Hertz,[8] who thought they were administering maximal doses by combining injections with suppositories, never mentioned the problem of an anesthetic effect from an overdose. Similarly, it is evidence of the extremely poor availability of the micropulverized progesterone that the researchers have administered hundreds of milligrams per day, without mentioning the symptoms of an overdose. Because of the difficulties involved in scientifically studying the clinical effectiveness of various formulations, I think the most practical way of evaluating the effectiveness of different progesterone formulations is to measure the amount extractable from the red blood cells, a few hours after the peak serum level has been reached. This will reasonably reflect the amounts reaching brain cells, adrenal glands, and the various other cells on which progesterone has its therapeutic action.

The Transparency of Life

Cataracts as a Model of Age-Related Disease

Ray Peat's Newsletter, 2006

In the markets around Lake Patzcuaro, they sell green transparent fish, about 6 inches long. When cooked, the meat is white, like ordinary fish. Most fish filets are a little translucent, but are at least cloudy, and usually pink by transmitted light. I don't know how the transparent fish work, because it seems that the blood and the network of blood vessels needed to sustain muscle activity would diffuse the light. Anyway, cooking disrupts the mysteriously ordered state of water and proteins that makes them transparent, roughly the way egg-white loses its transparency when it is cooked. I have never heard a convincing explanation for the opacity of cooked egg-white, either, but anything that disrupts the original structuring of the protein-water interaction will destroy the transparency.

Around 1970, I used a technique called nuclear magnetic resonance (NMR), which is the basis for the procedure known as MRI (magnetic resonance imaging), to compare the state of water in old (uterine) tissue and young tissue. Old tissue predictably contains less water than young tissue, but I found that the water in the old tissue was in a relatively free and uncontrolled state. When tissue swells and takes up water, more of the water is likely to be in this uncontrolled state, and this is one of the things that makes MRI so useful, because tumors, for example, show up vividly because of their large amount of uncontrolled ("unbound") water. I suspect that the measurements I made on uterine tissue showed a localized effect, that opposed the general trend toward increased dryness with aging. In the case of cataracts, this is clearly the case: Most of the lens becomes drier with age, but at a certain point there is a reversal, and some of the tissue takes up too much water. That's why I refer to cataracts as a model of age-related disease, rather than as a model of aging. In this sense, I am including them among the inflammatory diseases of aging—colitis, arthritis, and cancer, for example. MRI now can show developing cataracts before they are visible, because of increased water content in the area.

The lens of the eye is a fairly dense, tough, transparent living structure, which can develop opaque areas, cataracts, as a result of old age,

poisoning, radiation, disease, or trauma. The varieties of cataract relate to the causes. Most of the oxidative metabolism of the lens is in or near the epithelial layer that surrounds it. Old-age cataracts most often begin in this region.

Although the efficient oxidative energy metabolism occurs near the surface of the lens, there is a constant flow of fluid through the lens, entering it mainly in the front and back, and leaving on its "sides" or equator (considering the front and back as the poles, the direction light passes through). Oxygen and nutrients are supplied to the lens by way of this circulation of fluid, entering mostly from the aqueous humor in front (which also supplies the cornea), but also from the vitreous humor behind the lens.

When the flow of nutrients and energy is impaired, the organized state of the protein and water system in the cell is damaged, and an excess of water is taken up by the cells, as the protein content decreases. The loss of organization causes light to be dispersed, with a loss of transparency.

The lens of the eye is usually treated as something so specialized that it is hardly considered to be part of our living substance, just as dentistry has tended to treat teeth as inert things to be approached mechanically, rather than physiologically. The lens's circulatory system is very interesting, because of what it says about the nature of living substance. In the absence of blood vessels, it provides its own flow of nutrients. This flow is reminiscent of the flow of substances through the dentine channels of the teeth, through the axons of nerves (two-way transport in a very narrow channel), and, in some ways recalls the flow of fluids in plants, called "guttation" (drop formation), which is disturbing to botanists, because it is contrary to the textbook descriptions of proper physiology.

The flow of material through lens cells, dentine canals, and nerve axons should allow us to gain a perspective in which these observable processes become a model for other biological situations in which "transport" occurs: Kidney, intestine, or the skin of frogs, for example, in which water, ions, and other solutes are moved in considerable quantities.

When cells metabolize, they create gradients. In the cell, electrical, chemical, osmotic, and thermal gradients, for example, are constantly being produced or maintained. The whole substance of the cell is involved in its life processes. Because of prejudices introduced 200 years

ago, the life of the cell has been relegated to its "membrane" (where hypothetical "membrane pumps" reside) and its nucleus. When the term "cell" (hollow space) came into use instead of "corpuscle" (little body), a mind-set came into existence that discounted the importance of most of the living material, and claimed that it was a mere "random solution." Random solutions don't do much. The wonderful "membrane," under the direction of the nucleus (and its set of instructions), took care of everything.

Whenever assimilation or excretion took place, it was explained by inventing a property possessed by the cell "membranes." Therefore, we have physiology textbooks that have an unfounded explanation for everything. Before Copernicus, planetary movements were described as arbitrary "epicycles." They didn't make sense, but people studied them and felt that they were important. "Membrane physiology" is the modern equivalent of the Ptolemaic epicycles.

We know that glucose can be metabolized into pyruvic acid, which, in the presence of oxygen, can be metabolized into carbon dioxide. Without oxygen, pyruvic acid can be converted into lactic acid. The production of lactic acid tends to increase the pH inside the cell, and its excretion can lower the pH outside the cell.

The decrease of carbon dioxide that generally accompanies increased lactic acid, corresponds to increased intracellular pH. Carbon dioxide binds to many types of protein, for example by forming carbamino groups, changing the protein conformation, as well as its electrical properties, such as its isoelectric point. With increased pH, cell proteins become more strongly ionized, tending to separate, allowing water to enter the spaces, in the same way a gel swells in an alkaline solution.

The Bohr-Haldane effect describes the fact that hemoglobin releases oxygen in the presence of carbon dioxide, and releases carbon dioxide in the presence of oxygen. When oxygen is too abundant, it makes breathing more difficult, and one of its effects is to cause carbon dioxide to be lost rapidly. At high altitude, more carbon dioxide is retained, and this makes cellular respiration more efficient.

The importance of carbon dioxide to cell control process, and to the structure of the cell and the structure of proteins in general suggested that degenerative diseases would be less common at high altitude. Wounds and broken bones heal faster at high altitude, but the available

statistics are especially impressive in two of the major degenerative conditions, cancer and cataracts.

The two biggest studies of altitude and cataracts (involving 12,217 patients in one study, and 30,565 lifelong residents in a national survey in Nepal) showed a negative correlation between altitude and the incidence of cataract. At high altitude, cataracts appeared at a later age. In Nepal, an increase of a few thousand feet in elevation decreased the incidence of cataracts by 2.7 times. At the same time, it was found that exposure to sunlight increased the incidence of cataracts, and since the intensity of ultraviolet radiation is increased with altitude, this makes the decreased incidence of cataracts even more important.

All of the typical causes of cataracts, aging, poisons, and radiation, decrease the formation of carbon dioxide, and tend to increase the formation of lactic acid. Lactic acid excess is typically found in eyes with cataracts.

The electrical charge on the structural proteins will tend to increase in the presence of lactic acid or the deficiency of carbon dioxide, and the increase of charge will tend to increase the absorption of water.

The lens can survive for a considerable length of time *in vitro* (since it has its own circulatory system), so it has been possible to demonstrate that changes in the composition of the fluid can cause opacities to form, or to disappear.

Oxidants, including hydrogen peroxide which occurs naturally in the aqueous humor, can cause opacities to form quickly, but they will also disappear quickly in a solution that restores metabolic energy. The lens regulates itself powerfully; for example, it will swell when put into a hypotonic solution, but will quickly adapt, returning to approximately its normal size.

Several years ago, I saw what appeared to be oxidant-induced cataracts. Two women had a very sudden onset of cataracts, and I asked about their diet and supplements; it turned out that one of them had begun taking 500 mg of zinc daily a few months earlier, and the other had begun taking 600 mg of zinc and 250 mg of iron, on her doctor's recommendation, just a couple of months before the cataracts appeared.

For some reason, there have been many nutritional supplements sold as cataract remedies in the form of eye drops. I suppose a trace of the material could diffuse through the cornea into the aqueous humor, where it might make a difference in the lens's nutrient supply, but it

seems more reasonable to treat the body as a whole, nourishing every part in a balanced way.

Besides living at a high elevation or breathing extra carbon dioxide, the most certain way to increase the amount of carbon dioxide in the eye, and to prevent an excess of lactic acid, is to make sure that your thyroid function is adequate.

One man who took thyroid, USP, and vitamin E told me that his cataracts had regressed, but I haven't known other people who tried this.

If a person already has distinct cataracts, it might be worthwhile to experiment with a relatively high degree of hypercapnia, for example, breathing a 5 % mixture of CO_2 in air.

Carbon dioxide, at higher levels than are normal at sea level, has a profound effect on free radicals, reducing the free radical activity in the blood to approximately zero, before reaching the level that produces acidosis.

There are several situations in which carbon dioxide affects the hydration, water content, of biological materials, that I think give an insight into its effects on the lens. Hydrophilic glycoproteins are involved in each case. These are proteins with attached chains of sugar molecules that make them associate with a large amount of water. In the cornea, increased carbon dioxide strongly protects against swelling. The bulk of the cornea is a connective tissue that is relatively simple and passive compared to the compact cellular structure of the lens, and it is conventional to describe the thin layers of cells on the inside and outside of the cornea as being responsible for the water content of the underlying substance. However, even when the epithelial cells are removed, it has been demonstrated that carbon dioxide is able to prevent corneal swelling.[1]

Bronchial mucous secretions are an even simpler system, so it is very interesting that carbon dioxide is recognized as the most powerful regulator of their behavior. (This has important implications for "cystic fibrosis," or mucoviscidosis.)

> *"Among inhalants, steam and carbon dioxide have been found to be excellent expectorants. Relative humidity above 85 per cent liquefies sputum, decreases its viscosity..." "Carbon dioxide is the most effective agent of all. It not only lowers the viscosity of tenacious sputum, thereby facilitating expectora-*

> *tion, but it decreases the volume of sputum by promoting its active resorption by bronchial mucosa." "A five to ten per cent concentration of carbon dioxide is adequate and well tolerated if administered at intervals." "Oxygen has been shown to be an antiexpectorant and has effects opposite to those of carbon"*[2, p. 1068]

Oxygen tends to displace carbon dioxide from tissue, and is a source of free radicals.

One of the best-known free radical scavenging substances that has been widely used as a drug is iodide. It has been used to treat asthma, parasites, syphilis, cancer, Graves' disease, periodontal disease, and arteriosclerosis. Diseases that produce tissue overgrowth associated with inflammation—granulomas—have been treated with iodides, and although the iodide doesn't necessarily kill the germ, it does help to break down and remove the granuloma. Leprosy and syphilis were among the diseases involving granulomas that were treated in this way. In the case of tuberculosis, it has been suggested that iodides combine with unsaturated fatty acids which inhibit proteolytic enzymes, and thus allow for the removal of the abnormal tissue.

In experimental animals, iodide clearly delays the appearance of cataracts.[3]

Inflammation, edema, and free radical production are closely linked, and are produced by most things that interfere with energy production.

Endotoxin, produced by bacteria, mainly in the intestine, disrupts energy production, and promotes maladaptive inflammation. The wide spectrum of benefit that iodide has, especially in diseases with an inflammatory component, suggests first that it protects tissue by blocking free radical damage, but it also suggests the possibility that it might specifically protect against endotoxin.

There are subtler differences in transparence that probably have a variety of causes, but differences in water content or hydration might be involved in the lower transparency that has been seen in women's lenses. Estrogen, which tends to produce edema and hypotonic body fluids, also increases prolactin production. Prolactin is involved in water and electrolyte regulation, and it has been found to accelerate the development of experimental cataracts.[4] These hormones are associated with

the calcification of soft tissues, and cataracts contain very high levels of calcium.[5,6]

Estrogen is strongly associated with free radical processes, calcium mobilization, and acetylcholine release, all of which are involved in the process of excitoxicity.Alvarez, et al.,[7] have shown a possible involvement of acetylcholine in calcium mobilization in the lens.

Serotonin is another regulatory substance strongly associated with prolactin and estrogen, and it also can be involved in disrupting the metabolism of the lens. This is one of the potential dangers in using supplemental tryptophan.[8]

Old age commonly involves some changes in the color of tissues—loss of pigment from hair and skin, with appearance of new pigment (age pigment, lipofuscin), which may appear as "liver spots." But there is also a tendency of the toenails, fingernails, teeth, and lenses to turn yellow or brown. Some of this dark material seems to be age pigment, derived from unsaturated fatty acids, but other components have been identified, for example, tryptophan from damaged proteins. The Maillard reaction (similar to the browning that occurs in bread crust) has often been mentioned in relation to aging, and involves the combination of protein amino groups with sugars. But the browning of the lens tends to be associated with the general age related drying of the lens, it isn't irregularly distributed, and it doesn't significantly harm vision.

When I first heard about the age-related browning of the lens, I thought that the experience of colors would be affected, so I devised a test in which the relative darkness of blue and yellow could be judged in comparison with a graded strip of shades of grey.

After people of ages ranging from 10 to 80 had given exactly the same matches, I realized that the nervous system probably corrects for the "yellow filter" effect of the brown lens.

The browning of tissues will be the subject of another newsletter.

Among the interesting causes of cataracts: Tamoxifen and hypotonic fluids, sodium deficiency; toxicity of tryptophan; oxidants (metals, hydrogen peroxide, PUFA); diabetes, photosensitizers and sunlight; excess calcium, deficient magnesium. Excess cortisol. Radiation. Arachidonic and linoleic acids in other situations have been found to block cells' regulation of their water content. Hypothyroidism tends to increase the activity of serotonin, estrogen, prolactin, calcium, and the tendency of tissues to retain water, and to decrease the level of ATP.

Among the factors that probably have a role in preventing cataracts: Thyroid, progesterone, pregnenolone, vitamin E, iodide, pyruvate. Increasing the carbon dioxide lowers the cell's pH, and tends to resist swelling. Palmitic acid (a saturated fat that can be synthesized by our tissues) is normally oxidized by the lens. Calcium blockers experimentally prevent cataracts, suggesting that magnesium and thyroid (which also act to exclude calcium from cells) would have the same effect.

Thyroid hormone is essential for maintaining adequate carbon dioxide production, for minimizing lactic acid, cortisol and prolactin, for regulating calcium and magnesium, for avoiding hypotonicity of the body fluids, and for improving the ratio of palmitic acid to linoleic acid.

Thyroid, Insomnia, and the Insanities

Commonalities in Disease

Ray Peat's Newsletter, 2009

EVERYONE is familiar with the problem of defining insanity, in the case of people who plead innocent by reason of insanity. The official definition of insanity in criminal law is "the inability to tell right from wrong." Obviously, that can't be generalized to everyday life, because any sane person realizes that certainty is impossible, and that most situations, including elections, offer you at best the choice of "the lesser of two evils," or the opportunity to "do the right thing," and to "throw your vote away." People who persist in doing what they know is really right are "eccentric," in the sense that they don't adapt to society's norms. In a society that chooses to destroy ecosystems, rather than adapting to them, the question of sanity should be an everyday political issue.

The use of medical terms tends to give authority to the people who are in charge of defining the terms, and it can give the impression of objectivity when there really isn't any scientific validity behind the terms. In their historical senses, "crazy" (flawed) and "insane" (unsound) are probably more objective terms than the medically-invented terms, dementia praecox (premature idiocy) or schizophrenia (divided mind).

"Odd Speech" is one of the dimensions used in the diagnosis of insanity. I am reminded of William Wordsworth's dismissal of William Blake as insane after failing to understand some of Blake's poems—Wordsworth was conventional enough to become England's Poet Laureate, and to his limited perspective, Blake's clear verses were incomprehensibly odd.

Whenever a trusted government employee decides to blow the whistle on criminal activities, his agency invariably puts out the information that this now discharged employee is psychologically unbalanced. Dissent, in other words, is easy to dispose of by psychiatric tainting.

If we are going to speak of mental impairment, then we should have objective measures of what we are talking about. Blake unquestionably could do anything better than Wordsworth, because he was neither stupid nor dishonest, and it's almost a rule that ordinary employees are more competent than the administrators who evaluate their work. Ob-

jective standards of mental impairment would be more popular among patients than among diagnosticians, judges, and lawmakers.

In a famous test of the objectivity of diagnosis, a filmed interview with a patient was shown to British and U.S. psychiatrists. 69 % of the Americans diagnosed the patient as schizophrenic, but only 2 % of the British psychiatrists did.

The strictly medical/psychological definition of insanity is still, despite the existence of the International Classification of Diseases, and in the U.S. the Diagnostic and Statistical Manual, which enumerate a large number of "mental disorders," a crazily indefinite grouping of symptoms, and hasn't made diagnosis more objective. For example, in the last 30 years autism has been separated from childhood schizophrenia, but now the tendency is for both of them to be called developmental brain disorders. Both schizophrenia and autism are now often described in terms of a "spectrum of conditions," which hardly matters, since they are not understood in terms of cause, prevention, or cure.

The problem is in the history of psychosis as a medical idea. About 100 years ago, attempts were made to classify psychoses by their symptoms, unifying a great variety of old diagnostic categories into two groups, manic-depressive mood disorders, and "dementia praecox," or schizophrenia, which (as indicated by its name, premature dementia) was considered to be progressive and incurable. Several kinds of mental disorder were found to have clear causes, including vitamin deficiencies and various poisons and infections, but the idea of a certain thing called schizophrenia still persists.

The unitary concept of psychosis grew up in a culture in which "endogenous insanity" was a "hereditary taint," that for a time was "treated" by imprisonment, and that more recently has been treated with sterilization or euthanasia to eliminate the "insanity genes."

The idea that the disease is "in the genes" now serves the drug industry well, since they offer chemicals that will correct the specific "chemical error."

Not all psychiatrists and psychologists subscribed to the idea of a unitary psychosis, defined by a variety of symptoms. A positive contribution of Freudian psychoanalysis (and its congeners and competitors) was that it made people think in terms of causes and the possibility of cures, instead of hopelessness, stigmatization, isolation and eradication. Although Freud expressed the thought that biological causes and

cures would eventually be found, the profession he founded was not sympathetic to the idea of physiological therapies.

Looking for general physiological problems behind the various symptoms is very different from the practice of classifying the insanities according to their symptoms and the hypothetical "brain chemicals" that are believed to "cause the symptoms." The fact that some patients hallucinate caused many psychiatrists to believe that hallucinogenic chemicals, interfering with nerve transmitter substances such as dopamine or serotonin, were going to provide insight into psychotic states. The dopamine excess (or serotonin deficiency) theories developed at a time when only a few "transmitter substances" were known, and when they were thought to act as very specific on/off nerve switches, rather than as links in metabolic networks. The drug industry helps to keep those ideas alive.

The idea that the brain is like a computer, and that the nerves are like wires and switches, is behind all of the theories about transmitter substances and synapses. If this metaphor about the nature of the brain and the organism is fundamentally wrong, then the theories of schizophrenia based on nerve transmitter substances can hardly be right. Another theory of schizophrenia based on the computer metaphor has to do with the idea that nerve cells' wire-like and switch-like functions depend on their membranes, and, in the most popular version, that these all-important membranes are made of fish oil. The supporting evidence is supposed to be that the fish-oil-like fatty acids are depleted from the tissues of schizophrenics. Just looking at that point, the "evidence" is more likely to be the result of stress, which depletes unsaturated fatty acids, especially of the specified type, in producing lipid peroxides and other toxic molecules.

In one of its variations, the "essential fatty acid deficiency" doctrine suggests that a certain prostaglandin deficiency is the cause of schizophrenia, but experiments have shown that an excess of that prostaglandin mimics the symptoms of psychosis.

The drug industry's effect on the way the organism is commonly understood has been pervasively pathological. For example, the dogma about "cell surface receptors" has sometimes explicitly led people to say that the "brain chemicals" are active only at the surface of cells, and not inside the cells.

The consequences of this mistake have been catastrophic. For example, serotonin's precursor, tryptophan, and the drugs called "serotonin

reuptake inhibitors," and other serotonergic drugs, and serotonin itself, are carcinogenic and/or tumor promoters. Excessive serotonin is a major factor in kidney and heart failure, liver and lung disease, stroke, pituitary abnormalities, inflammatory diseases, practically every kind of sickness, at the beginning, middle, and end of life. In the brain, serotonin regulates circulation and mitochondrial function, temperature, respiration and appetite, alertness and learning, secretion of prolactin, growth hormones and stress hormones, and participates in the most complex biochemical webs. But the pharmaceutical industry's myth has led people to believe that serotonin is the chemical of happiness, and that tryptophan is its benign nutritional precursor, and that they are going to harmlessly influence the "receptors on nerve membranes."

A particular drug has many effects other than those that are commonly recognized as its "mechanism of action," but when an "antidepressant" or a "tranquilizer" or a "serotonin reuptake inhibitor" alleviates a particular condition, some people argue that the condition must have been caused by the "specific chemistry" that the drug is thought to affect. Because of the computer metaphor for the brain, these effects are commonly thought to be primarily in the synapses, the membranes, and the transmitter chemicals.

The argument for a "genetic" cause of schizophrenia relies heavily on twin studies in which the frequency of both twins being schizophrenic is contrasted to the normal incidence of schizophrenia in the population, which is usually about 1 %. There is a concordance of 30 % to 40 % between monozygotic (identical) twins, and a 5 % to 10 % concordance between fraternal twins, and both of these rates are higher than that of other siblings in the same family. That argument neglects the closer similarity of the intrauterine conditions experienced by twins, for example the sharing of the same placenta, and experiencing more concordant biochemical interactions between fetus and mother.

Defects of the brain, head, face, and even hands and fingerprints are seen more frequently in the genetically identical twin who later develops schizophrenia than the twin who doesn't develop schizophrenia. Of the twins, it is the baby with the lower birth weight and head size that is at a greater risk of developing schizophrenia.

Oliver Gillie (in his book, *Who Do You Think You Are?*) discussed some of the fraud that has occurred in twin studies, but no additional fraud is needed when the non-genetic explanation is simply ignored and

excluded from discussion. The editors of most medical and scientific journals are so convinced of the reality of genetic determination that they won't allow their readers to see criticisms of it.

Prenatal malnutrition or hormonal stress or other stresses are known to damage the brain, and especially its most highly evolved and metabolically active frontal lobes, and to reduce its growth, relative to the rest of the body.

The standard medical explanation for the association of pregnancy toxemia and eclampsia with birth defects has been, until recently, that both mother and child were genetically inferior, and that the defective child created the pregnancy sickness. The same "reasoning" has been invoked to explain the association of birth complications with later disease: The defective baby was the cause of a difficult birth. That argument has recently been discredited.[1]

Schizophrenics are known to have had a higher rate of obstetrical complications, including oxygen deprivation and Cesarian deliveries, than normal people. Like people with Alzheimer's disease, the circumference of their heads at birth was small, in proportion to their body weight and gestational age.

Animal studies show that perinatal brain problems tend to persist, influencing the brain's metabolism and function in adulthood.

Like the other major brain diseases, shizophrenia involves a low metabolic rate in crucial parts of the brain. In schizophrenics, "hypofrontality," low metabolism of the frontal lobes, is characteristic, along with abnormal balance between the hemispheres, and other regional imbalances.

A very important form of prenatal stress occurs in toxemia and preeclampsia, in which estrogen is dominant, and endotoxin and serotonin create a stress reaction with hypertension and impaired blood circulation to the uterus and placenta.

The brain, just like any organ or tissue, is an energy-producing metabolic system, and its oxidative metabolism is extremely intense, and it is more dependent on oxygen for continuous normal functioning than any other organ. Without oxygen, its characteristic functioning (consciousness) stops instantly (when blood flow stops, blindness begins in about three seconds, and other responses stop after a few more seconds). The concentration of ATP, which is called the cellular energy molecule, doesn't decrease immediately. Nothing detectable happens

to the "neurotransmitters, synapses, or membrane structures" in this short period; consciousness is a metabolic process that, in the computer metaphor, would be the flow of electrons itself, under the influence of an electromotive force, a complex but continuous sort of electromagnetic field. The computer metaphor would seem to have little to offer for understanding the brain.

In this context, I think it's necessary, for the present, to ignore the diagnostic details, the endless variety of qualifications of the idea of "schizophrenia," that fill the literature. Those diagnostic concepts seem to tempt people to look for "the precise cause of this particular subcategory" of schizophrenia, and to believe that a specific drug or combination of drugs will be found to treat it, while encouraging them to ignore the patient's physiology and history.

If we use the standard medical terms at all, it should be with the recognition that they are, in their present and historical form, not scientifically meaningful.

The idea that schizophrenia is a disease in itself tends to distract attention from the things it has in common with Alzheimer's disease, autism, depression, mania, the manic-depressive syndrome, the hyperactivity-attention deficit syndrome, and many other physical and mental problems. When brain abnormalities are found in "schizophrenics" but not in their normal siblings, it could be tempting to see the abnormalities as the "cause of schizophrenia," unless we see similar abnormalities in a variety of sicknesses.

For the present, it's best to think first in the most general terms possible, such as a "brain stress syndrome," which will include brain aging, stroke, altitude sickness, seizures, malnutrition, poisoning, the despair brought on by inescapable stress, and insomnia, which are relatively free of culturally arbitrary definitions. Difficulty in learning, remembering, and analyzing are objective enough that it could be useful to see what they have to do with a "brain stress syndrome."

Stress damages the energy producing systems of cells, especially the aerobic mitochondria, in many ways, and this damage can often be repaired. The insanities that are most often called schizophrenia tend to occur in late adolescence, or around menopause, or in old age, which are times of stress, especially hormonal stress. Post-partum psychosis often has features that resemble schizophrenia.

Although the prenatal factors that predispose a person toward the brain stress syndrome, and those that trigger specific symptoms later in life, might seem to be utterly different, the hormonal and biochemical reactions are probably closely related, involving the adaptive responses of various functional systems to the problem of insufficient adaptive ability and inadequate energy.

By considering cellular energy production, local blood flow, and the systemic support system, we can get insight into some of the biochemical events that are involved in therapies that are sometimes successful. A unified concept of health and disease will help to understand both the origins and the appropriate treatments for a great variety of brain stress syndromes.

The simple availability of oxygen, and the ability to use it, are regulated by carbon dioxide and serotonin, which act in opposite directions. Carbon dioxide inhibits the release of serotonin. Carbon dioxide and serotonin are regulated most importantly by thyroid function. Hypothyroidism is characterized by increased levels of both noradrenalin and serotonin, and of other stress-related hormones, including cortisol and estrogen. Estrogen shifts the balance of the "neurotransmitters" in the same direction, toward increased serotonin and adrenalin, for example by inhibiting enzymes that degrade the monoamine "neurotransmitters."

When an animal such as a squirrel approaches hibernation and is producing less carbon dioxide, the decrease in carbon dioxide releases serotonin, which slows respiration, lowers temperature, suppresses appetite, and produces torpor.

But in energy-deprived humans, increases of adrenalin oppose the hibernation reaction, alter energy production and the ability to relax, and to sleep deeply and with restorative effect.

In several ways, torpor is the opposite of sleep. Rapid eye movement (REM), that occurs at intervals during sleep and in association with increased respiration, disappears when the brain of a hibernating animal falls below a certain temperature. But torpor isn't like "non-REM" deep sleep, and in fact seems to be like wakefulness, in the sense that a sleep-debt is incurred: Hibernating animals periodically come out of torpor so they can sleep, and in those periods, when their temperature rises sharply, they have a very high percentage of deep "slow wave sleep."

Although it is common to speak of sleep and hibernation as variations on the theme of economizing on energy expenditure, I suspect

that nocturnal sleep has the special function of minimizing the stress of darkness itself, and that it has subsidiary functions, including its now well confirmed role in the consolidation and organization of memory. This view of sleep is consistent with observations that disturbed sleep is associated with obesity, and that the torpor-hibernation chemical, serotonin, powerfully interferes with learning.

Babies spend most of their time sleeping, and during life the amount of time spent sleeping decreases, with nightly sleeping time decreasing by about half an hour per decade after middle age. Babies have an extremely high metabolic rate and a stable temperature. With age the metabolic rate progressively declines, and as a result the ability to maintain an adequate body temperature tends to decrease with aging.

(The simple fact that body temperature regulates all organic functions, including brain waves, is habitually overlooked. The actions of a drug on brain waves, for example, may be mediated by its effects on body temperature, but this wouldn't be very interesting to pharmacologists looking for "transmitter-specific" drugs.)

Torpor is the opposite of restful sleep, and with aging, depression, hypothyroidism, and a variety of brain syndromes, sleep tends toward the hypothermic torpor.

An individual cell behaves analogously to the whole person. A baby's "high energy resting state" is paralleled by the stable condition of a cell that is abundantly charged with energy; ATP and carbon dioxide are at high levels in these cells. Progesterone's effects on nerve cells include favoring the high energy resting state, and this is closely involved in progesterone's "thermogenic" effect, in which it raises the temperature set-point.

The basal metabolic rate, which is mainly governed by thyroid, roughly corresponds to the average body temperature. However, in hypothyroidism, there is an adaptive increase in the activity of the sympathetic nervous system, producing more adrenalin, which helps to maintain body temperature by causing vasoconstriction in the skin. In aging, menopause, and various stressful conditions, the increased adrenalin (and the increased cortisol production which is produced by excess adrenalin) causes a tendency to wake more easily, and to have less restful sleep.

While the early morning body temperature will sometimes be low in hypothyroidism, I have found many exceptions to this. In protein defi-

ciency, sodium deficiency, in menopause with flushing symptoms, and in both phases of the manic depression cycle, and in some schizophrenics, the morning temperature is high, corresponding to very high levels of adrenalin and cortisol. Taking the temperature before and after breakfast will show a reduction of temperature, the opposite of what occurs in simple hypothyroidism, because raising the blood sugar permits the adrenalin and cortisol to fall.

The characteristic sleep pattern of hypothyroidism and old age is similar to the pattern seen in schizophrenia and depression, a decrease of deep slow wave sleep. Serotonin, like torpor, produces a similar effect. In other words, a torpor-like state can be seen in all of these brain-stress states. Several studies have found that anti-serotonin drugs improve sleep, and also reduce symptoms of schizophrenia and depression. It is common for the "neuroleptic" drugs to raise body temperature, even pathologically as in the "neuroleptic malignant syndrome."

In old people, who lose heat easily during the day, their extreme increase in the compensatory nervous and hormonal adrenalin activity causes their night-time heat regulation (vasoconstriction in the extremities) to rise to normal.

Increased body temperature improves sleep, especially the deep slow wave sleep. A hot bath, or even warming the feet, has the same effect as thyroid in improving sleep. Salty and sugary foods taken at bedtime, or during the night, help to improve the quality and duration of sleep. Both salt and sugar lower the adrenalin level, and both tend to raise the body temperature.

Hypothyroidism tends to cause the blood and other body fluids to be deficient in both sodium and glucose. Consuming salty carbohydrate foods momentarily makes up to some extent for the thyroid deficiency.

In the periodic table of the elements, lithium is immediately above sodium, meaning that it has the chemical properties of sodium, but with a smaller atomic radius, which makes its electrical charge more intense. Its physiological effects are so close to sodium's that we can get clues to sodium's actions by watching what lithium does.

Chronic consumption of lithium blocks the release of adrenalin from the adrenal glands, and it also has extensive antiserotonin effects, inhibiting its release from some sites, and blocking its actions at others.

Lithium forms a complex with the ammonia molecule, and since the ammonia molecule mimics the effects of serotonin, especially in fatigue,

this could be involved in lithium's antiserotonergic effects. Ammonia, like serotonin, impairs mitochondrial energy production (at a minimum, it uses energy in being converted to urea), so anti-ammonia, antiserotonin agents make more energy available for adaptation. Lithium has been demonstrated to restore the energy metabolism of mitochondria.[2]

Therapies that have been successful in treating "schizophrenia" include penicillin, sleep therapy, hyperbaric oxygen, carbon dioxide therapy, thyroid, acetazolamide, lithium and vitamins. These all make fundamental contributions to the restoration of biological energy. Antibiotics, for example, lower endotoxin formation in the intestine, protect against the induction by endotoxin of serotonin, histamine, estrogen, and cortisol. Acetazolamide causes the tissues to retain carbon dioxide, and increased carbon dioxide acidifies cells, preventing serotonin secretion.

Thyroid

Therapies, Confusion, and Fraud

Ray Peat's Newsletter, 2006

I. Respiratory-Metabolic Defect

BRODA Barnes, more than 60 years ago, summed up the major effects of hypothyroidism on health very neatly when he pointed out that if hypothyroid people don't die young from infectious diseases, such as tuberculosis, they die a little later from cancer or heart disease. He did his PhD research at the University of Chicago, just a few years after Otto Warburg, in Germany, had demonstrated the role of a "respiratory defect" in cancer. At the time Barnes was doing his research, hypothyroidism was diagnosed on the basis of a low basal metabolic rate, meaning that only a small amount of oxygen was needed to sustain life. This deficiency of oxygen consumption involved the same enzyme system that Warburg was studying in cancer cells.

Barnes experimented on rabbits, and found that when their thyroid glands were removed, they developed atherosclerosis, just as hypothyroid people did. By the mid-1930s, it was generally known that hypothyroidism causes the cholesterol level in the blood to increase; hypercholesterolemia was a diagnostic sign of hypothyroidism. Administering a thyroid supplement, blood cholesterol came down to normal exactly as the basal metabolic rate came up to the normal rate. The biology of atherosclerotic heart disease was basically solved before the second world war.

Many other diseases are now known to be caused by respiratory defects. Inflammation, stress, immunodeficiency, autoimmunity, developmental and degenerative diseases, and aging, all involve significantly abnormal oxidative processes. Just brief oxygen deprivation triggers processes that lead to lipid peroxidation, producing a chain of other oxidative reactions when oxygen is restored. The only effective way to stop lipid peroxidation is to restore normal respiration.

Now that dozens of diseases are known to involve defective respiration, the idea of thyroid's extremely broad range of actions is becoming easier to accept.

II. 50 Years of Commercially Motivated Fraud

Until the second world war, hypothyroidism was diagnosed on the basis of BMR (basal metabolic rate) and a large group of signs and symptoms. In the late 1940s, promotion of the (biologically inappropriate) PBI (protein-bound iodine) blood test in the U.S. led to the concept that only 5 % of the population were hypothyroid, and that the 40 % identified by "obsolete" methods were either normal, or suffered from other problems such as sloth and gluttony, or "genetic susceptibility" to disease. During the same period, thyroxine became available, and in healthy young men it acted "like the thyroid hormone." Older practitioners recognized that it was not metabolically the same as the traditional thyroid substance, especially for women and seriously hypothyroid patients, but marketing, and its influence on medical education, led to the false idea that the standard Armour thyroid USP wasn't properly standardized, and that certain thyroxine products were; despite the fact that both of these were shown to be false.

By the 1960s, the PBI test was proven to be irrelevant to the diagnosis of hypothyroidism, but the doctrine of 5 % hypothyroidism in the populaton became the basis for establishing the norms for biologically meaningful tests when they were introduced.

Meanwhile, the practice of measuring serum iodine, and equating it with "thyroxine the thyroid hormone," led to the practice of examining only the iodine content of the putative glandular material that was offered for sale as thyroid USP. This led to the substitution of materials such as iodinated casein for desiccated thyroid in the products sold as thyroid USP. The US FDA refused to take action, because they held that a material's iodine content was enough to identify it as "thyroid USP." In this culture of misunderstanding and misrepresentation, the mistaken idea of hypothyroidism's low incidence in the population led to the acceptance of dangerously high TSH (thyroid stimulating hormone) activity as "normal." Just as excessive FSH (follicle stimulating hormone) has been shown to have a role in ovarian cancer, excessive stimulation by TSH produces disorganization in the thyroid gland.

III. Tests & the "Free Hormone Hypothesis"

After radioactive iodine became available, many physicians would administer a dose, and then scan the body with a Geiger counter, to see

if it was being concentrated in the thyroid gland. If a person had been eating iodine-rich food (and iodine was used in bread as a preservative/dough condition, and was present in other foods as an accidental contaminant), they would already be over saturated with iodine, and the gland would fail to concentrate the iodine. The test can find some types of metastatic thyroid cancer, but the test generally wasn't used for that purpose. Another expensive and entertaining test has been the thyrotropin release hormone (TRH) test, to see if the pituitary responds to it by increasing TSH production. A recent study concluded that "TRH test gives many misleading results and has an elevated cost/benefit ratio as compared with the characteristic combination of low thyroxinemia and non-elevated TSH."[1] But the technological drama, cost, and danger[2] of this test is going to make it stay popular for a long time. If the special value of the test is to diagnose a pituitary abnormality, it seems intuitively obvious that overstimulating the pituitary might not be a good idea (e.g., it could cause a tumor to grow).

Everything else being equal, as they say, looking at the amount of thyroxine and TSH in the blood can be informative. The problem is that it's just a matter of faith that "everything else" is going to be equal. The exceptions to the "rule" regarding normal ranges for thyroxine and TSH have formed the basis for some theories about "the genetics of thyroid resistance," but others have pointed out that, when a few other things are taken into account, abnormal numbers for T_4, T_3, TSH, can be variously explained.

The actual quantity of T_3, the active thyroid hormone, in the blood can be measured with reasonable accuracy (using radioimmunoassay, RIA), and this single test corresponds better to the metabolic rate and other meaningful biological responses than other standard tests do. But still, this is only a statistical correspondence, and it doesn't indicate that any particular number is right for a particular individual.

Sometimes, a test called the RT_3U, or resin T_3 uptake, is used, along with a measurement of thyroxine. A certain amount of radioactive T_3 is added to a sample of serum, and then an adsorbent material is exposed to the mixture of serum and radioactive T_3. The amount of radioactivity that sticks to the resin is called the T_3 uptake. The lab report then gives a number called T_7, or free thyroxine index. The closer this procedure is examined, the sillier it looks, and it looks pretty silly on its face. The idea that the added radioactive T_3 that sticks to a piece of resin will correspond

to "free thyroxine," is in itself odd, but the really interesting question is, what do they mean by "free thyroxine"? Thyroxine is a fairly hydrophobic (insoluble in water) substance, that will associate with proteins, cells, and lipoproteins in the blood, rather than dissolving in the water. Although the Merck Index describes it as "insoluble in water," it does contain some polar groups that, in the right (industrial or laboratory) conditions, can make it slightly water soluble. This makes it a little different from progesterone, which is simply and thoroughly insoluble in water, though the term "free hormone" is often applied to progesterone, as it is to thyroid. In the case of progesterone, the term "free progesterone" can be traced to experiments in which serum containing progesterone (bound to proteins) is separated by a (dialysis) membrane from a solution of similar proteins which contain no progesterone. Progesterone "dissolves in" the substance of the membrane, and the serum proteins, which also tend to associate with the membrane, are so large that they don't pass through it. On the other side, proteins coming in contact with the membrane pick up some progesterone. The progesterone that passes through is called "free progesterone," but from that experiment, which gives no information on the nature of the interactions between progesterone and the dialysis membrane, or about its interactions with the proteins, or the proteins' interactions with the membrane, nothing is revealed about the reasons for the transmission or exchange of a certain amount of progesterone. Nevertheless, that type of experiment is used to interpret what happens in the body, where there is nothing that corresponds to the experimental set-up, except that some progesterone is associated with some protein.

The idea that the "free hormone" is the active form has been tested in a few situations, and in the case of the thyroid hormone, it is clearly not true for the brain, and some other organs. The protein-bound hormone is, in these cases, the active form; the associations between the "free hormone" and the biological processes and diseases will be completely false, if they are ignoring the active forms of the hormone in favor of the less active forms. The conclusions will be false, as they are when T_4 is measured, and T_3 ignored. Thyroid-dependent processes will appear to be independent of the level of thyroid hormone; hypothyroidism could be called hyperthyroidism.

Although progesterone is more fat soluble than cortisol and the thyroid hormones, the behavior of progesterone in the blood illustrates

some of the problems that have to be considered for interpreting thyroid physiology. When red cells are broken up, they are found to contain progesterone at about twice the concentration of the serum. In the serum, 40 to 80 % of the progesterone is probably carried on albumin. (Albumin easily delivers its progesterone load into tissues.) Progesterone, like cholesterol, can be carried on/in the lipoproteins, in moderate quantities. This leaves a very small fraction to be bound to the "steroid binding globulin." Anyone who has tried to dissolve progesterone in various solvents and mixtures knows that it takes just a tiny amount of water in a solvent to make progesterone precipitate from solution as crystals; its solubility in water is essentially zero. "Free" progesterone would seem to mean progesterone not attached to proteins or dissolved in red blood cells or lipoproteins, and this would be zero. The tests that purport to measure free progesterone are measuring something, but not the progesterone in the watery fraction of the serum.

The thyroid hormones associate with three types of simple proteins in the serum: Transthyretin (prealbumin), thyroid binding globulin, and albumin. A very significant amount is also associated with various serum lipoproteins, including HDL, LDL, and VLDL (very low density lipoproteins). A very large portion of the thyroid in the blood is associated with the red blood cells. When red cells were incubated in a medium containing serum albumin, with the cells at roughly the concentration found in the blood, they retained T_3 at a concentration 13.5 times higher than that of the medium. In a larger amount of medium, their concentration of T_3 was 50 times higher than the medium's. When laboratories measure the hormones in the serum only, they have already thrown out about 95 % of the thyroid hormone that the blood contained.

The T_3 was found to be strongly associated with the cells' cytoplasmic proteins, but to move rapidly between the proteins inside the cells and other proteins outside the cells.

When people speak of hormones travelling "on" the red blood cells, rather than "in" them, it is a concession to the doctrine of the impenetrable membrane barrier.

Much more T_3 bound to albumin is taken up by the liver than the small amount identified *in vitro* as free T_3.[3] The specific binding of T_3 to albumin alters the protein's electrical properties, changing the way the albumin interacts with cells and other proteins. (Albumin becomes electrically more positive when it binds the hormone; this would make

the albumin enter cells more easily. Giving up its T_3 to the cell, it would become more negative, making it tend to leave the cell.) This active role of albumin in helping cells take up T_3 might account for its increased uptake by the red cells when there were fewer cells in proportion to the albumin medium. This could also account for the favorable prognosis associated with higher levels of serum albumin in various sicknesses.

When T_3 is attached chemically (covalently, permanently) to the outside of red blood cells, apparently preventing its entry into other cells, the presence of these red cells produces reactions in other cells that are the same as some of those produced by the supposedly "free hormone." If T_3 attached to whole cells can exert its hormonal action, why should we think of the hormone bound to proteins as being unable to affect cells? The idea of measuring the "free hormone" is that it supposedly represents the biologically active hormone, but in fact it is easier to measure the biological effects than it is to measure this hypothetical entity. Who cares how many angels might be dancing on the head of a pin, if the pin is effective in keeping your shirt closed?

IV. Events in the Tissues

Besides the effects of commercial deception, confusion about thyroid has resulted from some biological clichés. The idea of a "barrier membrane" around cells is an assumption that has affected most people studying cell physiology, and its effects can be seen in nearly all of the thousands of publications on the functions of thyroid hormones. According to this idea, people have described a cell as resembling a droplet of a watery solution, enclosed in an oily bag which separates the internal solution from the external watery solution. The cliché is sustained only by neglecting the fact that proteins have a great affinity for fats, and fats for proteins; even soluble proteins, such as serum albumin, often have interiors that are extremely fat-loving. Since the structural proteins that make up the framework of a cell aren't "dissolved in water" (they used to be called "the insoluble proteins"), the lipophilic phase isn't limited to an ultramicroscopically thin surface, but actually constitutes the bulk of the cell.

Molecular geneticists like to trace their science from a 1944 experiment that was done by Avery., et al. Avery's group knew about an earlier experiment, that had demonstrated that when dead bacteria were added

to living bacteria, the traits of the dead bacteria appeared in the living bacteria. Avery's group extracted DNA from the dead bacteria, and showed that adding it to living bacteria transferred the traits of the dead organisms to the living.

In the 1930s and 1940s, the movement of huge molecules such as proteins and nucleic acids into cells and out of cells wasn't a big deal; people observed it happening, and wrote about it. But in the 1940s the idea of the barrier membrane began gaining strength, and by the 1960s nothing was able to get into cells without authorization. At present, I doubt that any molecular geneticist would dream of doing a gene transplant without a "vector" to carry it across the membrane barrier.

Since big molecules are supposed to be excluded from cells, it's only the "free hormone" which can find its specific port of entry into the cell, where another cliché says it must travel into the nucleus, to react with a specific site to activate the specific genes through which its effects will be expressed.

I don't know of any hormone that acts that way. Thyroid, progesterone, and estrogen have many immediate effects that change the cell's functions long before genes could be activated.

Transthyretin, carrying the thyroid hormone, enters the cell's mitochondria and nucleus.[4,5] In the nucleus, it immediately causes generalized changes in the structure of chromosomes, as if preparing the cell for major adaptive changes. Respiratory activation is immediate in the mitochondria, but as respiration is stimulated, everything in the cell responds, including the genes that support respiratory metabolism. When the membrane people have to talk about the entry of large molecules into cells, they use terms such as "endocytosis" and "translocases," that incorporate the assumption of the barrier. But people who actually investigate the problem generally find that "diffusion," "codiffusion," and absorption describe the situation adequately.[6,7] "Active transport" and "membrane pumps" are ideas that seem necessary to people who haven't studied the complex forces that operate at phase boundaries, such as the boundary between a cell and its environment.

V. Therapy

Years ago it was reported that Armour thyroid, U.S.P., released T_3 and T_4, when digested, in a ratio of 1:3, and that people who used it had

much higher ratios of T_3 to T_4 in their serum, than people who took only thyroxine. The argument was made that thyroxine was superior to thyroid U.S.P., without explaining the significance of the fact that healthy people who weren't taking any thyroid supplement had higher T_3:T_4 ratios than the people who took thyroxine, or that our own thyroid gland releases a high ratio of T_3 to T_4. The fact that the T_3 is being used faster than T_4, removing it from the blood more quickly than it enters from the thyroid gland itself, hasn't been discussed in the journals, possibly because it would support the view that a natural glandular balance was more appropriate to supplement than pure thyroxine.

The serum's high ratio of T_4 to T_3 is a pitifully poor argument to justify the use of thyroxine instead of a product that resembles the proportion of these substances secreted by a healthy thyroid gland, or maintained inside cells. About 30 years ago, when many people still thought of thyroxine as "the thyroid hormone," someone was making the argument that "the thyroid hormone" must work exclusively as an activator of genes, since most of the organ slices he tested didn't increase their oxygen consumption when it was added. In fact, the addition of thyroxine to brain slices suppressed their respiration by 6 % during the experiment. Since most T_3 is produced from T_4 in the liver, not in the brain, I think that experiment had great significance, despite the ignorant interpretation of the author. An excess of thyroxine, in a tissue that doesn't convert it rapidly to T_3, has an antithyroid action.[8] This happens in many women who are given thyroxine; as their dose is increased, their symptoms get worse.

The brain concentrates T_3 from the serum, and may have a concentration 6 times higher than the serum,[8] and it can achieve a higher concentration of T_3 than T_4. It takes up and concentrates T_3, while tending to expel T_4. Reverse T_3 (rT_3) doesn't have much ability to enter the brain, but increased T_4 can cause it to be produced in the brain. These observations suggest to me that the blood's T_3:T_4 ratio would be very "brain favorable" if it approached more closely to the ratio formed in the thyroid gland, and secreted into the blood. Although most synthetic combination thyroid products now use a ratio of four T_4 to one T_3, many people feel that their memory and thinking are clearer when they take a ratio of about three to one. More active metabolism probably keeps the blood ratio of T_3 to T_4 relatively high, with the liver consuming T_4 at about the same rate that T_3 is used.

Since T_3 has a short half life, it should be taken frequently. If the liver isn't producing a noticeable amount of T_3, it is usually helpful to take a few micrograms per hour. Since it restores respiration and metabolic efficiency very quickly, it isn't usually necessary to take it every hour or two, but until normal temperature and pulse have been achieved and stabilized, sometimes it's necessary to take it four or more times during the day. T_4 acts by being changed to T_3, so it tends to accumulate in the body, and on a given dose, usually reaches a steady concentration after about two weeks.

An effective way to use supplements is to take a combination T_4-T_3 dose, e.g., 40 μg of T_4 and 10 μg of T_3 once a day, and to use a few mcg of T_3 at other times in the day. Keeping a 14-day chart of pulse rate and temperature allows you to see whether the dose is producing the desired response. If the figures aren't increasing at all after a few days, the dose can be increased, until a gradual daily increment can be seen, moving toward the goal at the rate of about 1/14 per day

VI. Diagnosis

In the absence of commercial techniques that reflect thyroid physiology realistically, there is no valid alternative to diagnosis based on the known physiological indicators of hypothyroidism and hyperthyroidism. The failure to treat sick people because of one or another blood test that indicates "normal thyroid function," or the destruction of patients' healthy thyroid glands because one of the tests indicates hyperthyroidism, isn't acceptable just because it's the professional standard, and is enforced by benighted state licensing boards.

Toward the end of the twentieth century, there has been considerable discussion of "evidence-based medicine." Good judgment requires good information, but there are forces that would over-rule individual judgment as to whether published information is applicable to certain patients. In an atmosphere that sanctions prescribing estrogen or insulin without evidence of an estrogen deficiency or insulin deficiency, but that penalizes practitioners who prescribe thyroid to correct symptoms, the published "evidence" is necessarily heavily biased. In this context, "meta-analysis" becomes a tool of authoritarianism, replacing the use of judgment with the improper use of statistical analysis.

Unless someone can demonstrate the scientific invalidity of the methods used to diagnose hypothyroidism up to 1945, then they constitute the best present evidence for evaluating hypothyroidism, because all of the blood tests that have been used since 1950 have been shown to be, at best, very crude and conceptually inappropriate methods.

Thomas H. McGavack's 1951 book, *The Thyroid*, was representative of the earlier approach to the study of thyroid physiology. Familiarity with the different effects of abnormal thyroid function under different conditions, at different ages, and the effects of gender, were standard parts of medical education that had disappeared by the end of the century. Arthritis, irregularities of growth, wasting, obesity, a variety of abnormalities of the hair and skin, carotenemia, amenorrhea, tendency to miscarry, infertility in males and females, insomnia or somnolence, emphysema, various heart diseases, psychosis, dementia, poor memory, anxiety, cold extremities, anemia, and many other problems were known reasons to suspect hypothyroidism. If the physician didn't have a device for measuring oxygen consumption, estimated calorie intake could provide supporting evidence. The Achilles' tendon reflex was another simple objective measurement with a very strong correlation to the basal metabolic rate. Skin electrical resistance, or whole body impedance wasn't widely accepted, though it had considerable scientific validity.

A therapeutic trial was the final test of the validity of the diagnosis: If the patient's symptoms disappeared as his temperature and pulse rate and food intake were normalized, the diagnostic hypothesis was confirmed. It was common to begin therapy with one or two grains of thyroid, and to adjust the dose according to the patient's response. Whatever objective indicator was used, whether it was basal metabolic rate, or serum cholesterol, or core temperature, or reflex relaxation rate, a simple chart would graphically indicate the rate of recovery toward normal health.

Tissue-Bound Estrogen in Aging

Ray Peat's Newsletter, 2006

DOCTRINES are admitted into the "scientific canon" by those who have the power of censorship. In astronomy, Halton Arp's discovery of "anomalous" galactic red-shifts is practically unknown, because the journal editors say the observations are "just anomalies," or that the theories which could explain them are unconventional; but the actual problem is that they are strong evidence against The Big Bang, Hubble's Law, and the Expanding Universe. American science, since the 1940s, has probably been the most censored and doctrinaire in the world.

Gilbert Ling's revolution in cell biology remains outside the canon, despite the profound influence of MRI, which grew directly out of his view of the cell, because his work provided conclusive evidence that cells are not regulated by "semipermeable membranes and membrane pumps." Every field of science is ruled by a doctrinaire establishment.

Charles E. Brown-Séquard (1817–94) was a physiologist who pioneered scientific endocrinology, but who was ridiculed because of his claim that extracts of animal glands had an invigorating effect when injected. His place in the scientific canon is mainly as an object of ridicule, and the details of his case are perfectly representative of the way our "canon" has been constructed. The argument for dismissing his observations was that he used a water extract of testicles, and, according to the 20th century American biologists, testosterone is not water soluble, and so the water extract would have "contained no hormone." The argument is foolish, because living organs contain innumerable substances that will solublize oily molecules, but also because Brown-Sequard was describing an effect that wasn't necessarily limited to a single chemical substance. (The transplanting of living cells to repair tissues is finally being accepted, but the pioneers in promoting tissue regeneration or repair with the transplantation of living, dead, or stressed cells—V. Filatov, L.V. Polezhaev, W.T. Summerlin, for example—were simply written out of history.)

If Brown-Séquard's extract couldn't work because testosterone isn't soluble in water, then what are we to think of the thousands of medical publications that talk about "free hormones" as the only active hormones? ("Free hormone" is defined as the hormone that isn't bound to a

transporting protein, with the more or less explicit idea that it is dissolved in the water of the plasma or extracellular fluid.) Brown-Séquard's tissue extracts would have contained solublizing substances including proteins and phospholipids, so the oily hormones would certainly be present (and active) in his extracts. But the thousands of people who ridiculed him committed themselves to the fact that steroid hormones are insoluble in water. By their own standard, they are selling an impossibility when they do calculations to reveal the amount of "free hormone," as something distinct from the protein bound hormone, in the patient's blood.

The immense Hormone Replacement Therapy industry—which Brown-Séquard's experiments foreshadowed—is based on the fact that the concentrations of some hormones in the blood serum decrease with aging.

At first, it was assumed that the amount of the hormone in the blood corresponded to the effectiveness of that hormone. Whatever was in the blood was being delivered to the "target tissues." But as the idea of measuring "protein bound iodine" (PBI) to determine thyroid function came into disrepute (because it never had a scientific basis at all), new ideas of measuring "active hormones" came into the marketplace, and currently the doctrine is that the "bound" hormones are inactive, and the active hormones are "free." The "free" hormones are supposed to be the only ones that can get into the cells to deliver their signals, but the problem is that "free hormones" exist only in the imagination of people who interpret certain lab tests, as I discussed in the newsletter on thyroid tests (May, 2000).

In the 1960s and 1970s, when the PBI test was disappearing, there was intense interest in—a kind of mania regarding—the role of "membranes" in regulating cell functions, and the membrane was still seen by most biologists as the "semipermeable membrane" which, "obviously," would exclude molecules as large as albumin and the other proteins that carry thyroid and other hormones in the blood. (In reality, and experimental observations, albumin and other proteins enter cells more or less freely, depending on prevailing conditions.) The membrane doctrine led directly to the "free hormone" doctrine.

This issue, of arguing about which form of a hormone is the "active" form, has to do with explaining how much of the blood-carried hormone is going to get into the "target tissues." If the membrane is a "semipermeable" barrier to molecules such as hormones, then specific receptors and

transporters will be needed. If the concentration of a hormone inside the cell is higher than that in the blood, a "pump" will usually be invoked, to produce an "active transport" of the hormone against its concentration gradient.

But if the membrane regulates the passage of hormones from blood to tissue cells, and especially if pumps are needed to move the hormone into the cell, how relevant is the measurement of hormones in the blood?

Within the blood, progesterone and thyroid hormone (T_3) are much more concentrated in the red blood cells than in the serum. Since it isn't likely that red blood cells are "targets" for the sex hormones, or for progesterone or even thyroid, their concentration "against their gradient" in these cells suggests that a simple distribution by solubility is involved. Oily substances just naturally tend to concentrate inside cells because of their insolubility in the watery environment of the plasma and extracellular fluid. Proteins that have "oily" regions effectively bind oily molecules, such as fats and steroids. Even red blood cells have such proteins.

In the case of oil soluble molecules, such as progesterone and estrogen, it's important to explain that most of their "binding" to proteins or other oil-loving molecules is really the nearly passive consequence of the molecules' being forced away from the watery phase—they are hydrophobic, and although it would take a great amount of energy to make these insoluble substances enter the watery phase, the attractive force between them and the cell is usually small. This means that they can be freely mobile, while "bound" or concentrated within the cell. The oxygen atoms, and especially the phenolic group of estrogen, slightly reduce the hormones' affinity for simple oils, but they interact with other polar or aromatic groups, giving estrogen the ability to bind more strongly and specifically with some proteins and other molecules. Enzymes which catalyze estrogen's oxidation-reduction actions are among the specific estrogen-binding proteins.

Many proteins and lipoproteins bind steroids, but some intracellular proteins bind them so strongly that they have been—in a very teleological, if not anthropomorphic, way—considered as the switch by which the hormone turns on the cellular response. In the popular doctrine of the Estrogen Receptor, a few molecules of estrogen bind to the receptors, which carry them to the nucleus of the cell, where the activated receptors turn on the genes in charge of the female response.

(Or the male response, or the growth response, or the atrophy response, or whatever genetic response estrogen is producing.) Once the switch has been thrown, the estrogen molecules have fulfilled their hormonal duty, and must get lost, so that the response isn't perpetuated indefinitely by a few molecules.

Although the Estrogen Receptor doctrine is worse than silly, there are real proteins which bind estrogen, and some of these are called receptors. The uterus, breast, and brain, which are very responsive to estrogen, bind, or concentrate, estrogen molecules.

When I was working on my dissertation, I tried to extract estrogens from hamster uteri, but the chemical techniques I was using to measure estrogen weren't accurate for such small quantities. A few years later, S. Batra was able to extract the estrogen from human tissue in quantities large enough for accurate analysis by radioimmunoassay.[1]

His crucial observation was that the difference in estrogen concentration between tissue and blood was lowest in the luteal phase, when progesterone is high:

"The tissue/plasma ratio of E_2 (estradiol) ranged from 1.45 to 20.36 with very high values in early follicular phase and the lowest in midluteal phase." This means that progesterone prevents the tissue from concentrating estrogen. He made similar observations during pregnancy, with tissue estrogen decreasing as blood progesterone increased, so that there is less estrogen in the tissue than in the plasma. But in women who aren't pregnant, and when their progesterone is low, the tissues may contain 20 to 30 times more estrogen than the plasma (in equal volumes).

In aging, the sharply decreased progesterone production creates a situation resembling the follicular phase of the menstrual cycle, allowing tissues to concentrate estrogen even when the serum estrogen may be low.

"In postmenopausal women, the tissue concentration of E_2 was not significantly lower than in menstruating women in follicular phase…"[2]

Besides the relatively direct actions of progesterone on the estrogen receptors, keeping their concentration low, and its indirect action by preventing prolactin from stimulating the formation of estrogen receptors, there are many other processes that can increase or decrease the tissue concentration of estrogen, and many of these influences change with aging.

There are two kinds of enzyme that produce estrogen. Aromatase converts male hormones into estrogen. Beta-glucuronidase converts the inactive estrogen-glucuronides into active estrogen. The healthy liver inactivates practically all the estrogen that reaches it, mostly by combining it with the "sugar acid," glucuronic acid. This makes the estrogen water soluble, and it is quickly eliminated in the urine. But when it passes through inflamed tissue, these tissues contain large amounts of beta-glucuronidase, which will remove the glucuronic acid, leaving the pure estrogen to accumulate in the tissue.

Many kinds of liver impairment decrease its ability to excrete estrogen, and estrogen contributes to a variety of liver diseases. The work of the Biskinds in the 1940s showed that a dietary protein deficiency prevented the liver from detoxifying estrogen. Hypothyroidism prevents the liver from attaching glucuronic acid to estrogen, and so increases the body's retention of estrogen, which in turn impairs the thyroid gland's ability to secrete thyroid hormone. Hypothyroidism often results from nutritional protein deficiency.

Although we commonly think of the ovaries as the main source of estrogen, the enzyme which makes it can be found in all parts of the body. Surprisingly, in rhesus monkeys, aromatase in the arms accounts for a very large part of estrogen production. Fat and the skin are major sources of estrogen, especially in older people. The activity of aromatase increases with aging, and under the influence of prolactin, cortisol, prostaglandin, and the pituitary hormones, FSH (follicle stimulating hormone) and growth hormone. It is inhibited by progesterone, thyroid, aspirin, and high altitude. Aromatase can produce estrogen in fat cells, fibroblasts, smooth muscle cells, breast and uterine tissue, pancreas, liver, brain, bone, skin, etc. Its action in breast cancer, endometriosis, uterine cancer, lupus, gynecomastia, and many other diseases is especially important. Aromatase in mammary tissue appears to increase estrogen receptors and cause breast neoplasia, independently of ovarian estrogen.[3]

Women who have had their ovaries removed are usually told that they need to take estrogen, but animal experiments consistently show that removal of the gonads causes the tissue aromatases to increase. The loss of progesterone and ovarian androgens is probably responsible for this generalized increase in the formation of estrogen. In the brain, aromatase increases under the influence of estrogen treatment.

Sulfatase is another enzyme that releases estrogen in tissues, and its activity is inhibited by antiestrogenic hormones.

In at least some tissues, progesterone inhibits the release or activation of beta-glucuronidase (which, according to Cristofalo and Kabakjian,[4] increases with aging). Glucaric acid, which inhibits this enzyme, is being used to treat breast cancer, and glucuronic acid also tends to inhibit the intracellular release of estrogen by beta-glucuronidase.

Although there is clearly a trend toward the rational use of antiestrogenic treatments for breast cancer, in other diseases the myth of estrogen deficiency still prevents even rudimentary approaches.

Ever since Lipshutz' work in the 1940s, it has been established that the uninterrupted effect of a little estrogen is more harmful than larger but intermittent exposures. But after menopause, when progesterone stops its cyclic displacement of estrogen from the tissues, the tissues retain large amounts of estrogen continuously.

The menopause itself is produced by the prolonged exposure to estrogen beginning in puberty, in spite of the monthly protection of the progesterone produced by cycling ovaries. The unopposed action of the high concentration of tissue-bound estrogen after menopause must be even more harmful.

The decline of the antiestrogenic factors in aging, combined with the increase of pro-estrogenic factors such as cortisol and prolactin and FSH, occurs in both men and women. During the reproductive years, women's cyclic production of large amounts of progesterone probably retards their aging enough to account for their greater longevity. Childbearing also has a residual antiestrogenic effect and is associated with increased longevity.

Being aware of this pervasive increase in estrogen exposure with aging should make it possible to marshal a comprehensive set of methods for opposing that trend toward degeneration.

Tryptophan, Serotonin, and Aging

Ray Peat's Newsletter, 2006

BEGINNING with the industrial production of glutamic acid (sold as MSG, monosodium glutamate), the public has been systematically misinformed about the effects of amino acids in the diet. The FDA has been industry's powerful ally in misleading the public. Despite research that clearly showed that adults assimilate whole proteins more effectively than free amino acids, much of the public has been led to believe that "predigested" hydrolized protein and manufactured free amino acids are more easily assimilated than real proteins, and that they are not toxic. Even if free amino acids could be produced industrially without introducing toxins and allergens, they wouldn't be appropriate for nutritional use.

Although some research shows that babies up to the age of 18 months can assimilate free amino acids, a baby formula containing hydrolyzed protein was associated with decreased serum albumin, which suggests that it interfered with protein synthesis.

The myth that free amino acids are "natural nutritional substances" has been used to promote the use of many products besides MSG, including aspartame, chelated minerals, and tryptophan.

Although several amino acids can be acutely or chronically toxic, even lethal, when too much is eaten, tryptophan is the only amino acid that is also carcinogenic. (It can also produce a variety of toxic metabolites, and it is very susceptible to damage by radiation.) Since tryptophan is the precursor of serotonin, the amount of tryptophan in the diet can have important effects on the way the organism responds to stress, and the way it develops, adapts, and ages.

When an inflammatory disease (eosinophilia-myalgia syndrome) was noticed in people using tryptophan tablets (1989–90), there was an intense campaign to exonerate the tryptophan itself by blaming the reaction on an impurity in one company's product. But the syndrome didn't occur only in the people who used that company's product, and similar changes can be produced by a high-tryptophan diet.[1]

There are people who advocate the use of tryptophan supplementation or other means to increase serotonin in the tissues as a treatment for the fibromyalgia syndrome, but the evidence increasingly suggests that

excessive serotonin, interfering with muscle mitochondria, is a major factor in the development of that syndrome.

In 1965, Hans Selye showed that the injection of serotonin caused muscular dystrophy. Subsequent studies suggest that serotonin excess is involved in both muscular and nervous dystrophy or degeneration.[2,3]

The fatigue produced by "over-training" is probably produced by a tryptophan and serotonin overload, resulting from catabolism of muscle proteins and stress-induced increases in serotonin. Muscle catabolism also releases a large amount of cysteine, and cysteine, methionine, and tryptophan suppress thyroid function.[4] Stress also liberates free fatty acids from storage, and these fatty acids increase the uptake of tryptophan into the brain, increasing the formation of serotonin. Since serotonin increases ACTH and cortisol secretion, the catabolic state tends to be self-perpetuating. This process is probably a factor influencing the rate of aging, and contributing to the physiological peculiarities of aging and depression.

Malnutrition, and specifically protein deficiency, produces an inflammatory state that involves extreme serotonin dominance. Stress or malnutrition prenatally or in infancy leads to extreme serotonin dominance in adulthood. Other functions of tryptophan are reduced, as more of it is turned into serotonin.

Decreasing tryptophan or decreasing serotonin improves learning and alertness, while increased serotonin impairs learning.

Tryptophan is an essential amino acid for reproduction and growth of the young animal. Most research on the nutritional requirements for amino acids has been done on farm animals, because of the economic incentive to find the cheapest way to produce the fastest growth. Farmers aren't interested in the nutritional factors that would produce the longest-lived pigs. Some research has been done on the amino acid requirements of rats over a significant part of their short lifespans. In rats and farm animals, the amount of tryptophan required decreases with time as the rate of growth slows.

In some ways, rats never really mature, since they keep growing for nearly their whole lifespan. Their growth stops just a short time before they die, which is usually around the age of two or three years. (At this age, rats' cells still retain approximately the same high water content seen in the cells of a two year-old child.) They usually become infertile about half-way through their lifespan. If we try to draw conclusions about

amino acid requirements from the rat studies, I think we would want to extrapolate the curve for the decreasing need for tryptophan, far beyond the point seen during the rat's short life. And those "requirements" were determined according to the amounts that produced a maximum rate of growth, using the index of the pig farmers, as if the rats were being studied for possible use as meat.

When rats were fed a diet completely lacking tryptophan for a short period, or a diet containing only one fourth of the "normal" amount for a more prolonged period, the results were surprising: They kept the ability to reproduce up to the age of 36 months (versus 17 months for the rats on the usual diet), and both their average longevity and their maximum longevity increased significantly. They looked and acted like younger rats. (A methionine-poor diet also has dramatic longevity-increasing effects.)

On the tryptophan-poor diet, the amount of serotonin in the brain decreased. When brain serotonin decreases, the level of testosterone in male animals increases. More than 20 years ago, a chemical (p-chlorophenylalanine) that inhibits serotonin synthesis was found to tremendously increase libido.

In old age, the amount of serotonin in the brain increases. This undoubtedly is closely related to the relative inability to turn off cortisol production that is characteristic of old age.[5] Hypothyroidism increases the formation of serotonin, as does cortisol.[6–8]

In white hair, the amount of tryptophan is higher than in hair of any other color. Although serotonin and tryptophan are very important during rapid growth, their presence in senile tissues is probably closely associated with the processes of decline. The hair loss that occurs in hypothyroidism, postpartum syndrome, and with the use of drugs such as St. John's wort (which can also cause the "serotonin syndrome") could be another effect of excess serotonin.

Serotonin stimulates cell division and tends to increase the formation of connective tissue, so its formation should be closely regulated once full growth is achieved. It contributes to the age- or stress-related thickening of blood vessels, and other fibrotic processes that impair organ function.

The metabolic rate (eating more without gaining extra weight) and ability to regulate body temperature are increased by early tryptophan deprivation.[9,10] The ability to oxidize sugar is impaired by serotonin, and

several drugs with antiserotonin actions are being used to treat diabetes and its complications, such as hypertension, obesity, and foot ulcers.

An excess of tryptophan early in life, stress, or malnutrition, activates the system for converting tryptophan into serotonin, and that tendency persists into adulthood, modifying pituitary function, and increasing the incidence of pituitary and other cancers.

Serotonin's contribution to high blood pressure is well established. It activates the adrenal cortex both directly and through activation of the pituitary. It stimulates the production of both cortisol and aldosterone. It also activates aldosterone secretion by way of the renin-angiotensin system. Angiotensin is an important promoter of inflammation, and contributes to the degeneration of blood vessels with aging and stress. It can also promote estrogen production.

In the traditional diet, rather than just eating muscle meats, all the animal parts were used. Since collagen makes up about 50% of the protein in an animal, and is free of tryptophan, this means that people were getting about half as much tryptophan in proportion to other amino acids when they used foods such as "head cheese," ox-tails, and chicken feet.

While some of the toxic effects of an excess of individual amino acids have been investigated, and some of the protective or harmful interactions resulting from changing the ratios of the amino acids have been observed, the fact that there are about 20 amino acids in our normal diet means that there is an enormous number of possibilities for harmful or beneficial interactions.

The optimal quantity of protein in the diet has traditionally been treated as if it were a matter that could be resolved just by observing the rate of growth when a certain protein is given in certain quantities, along with "standard amounts" of calories and other nutrients. This kind of research has been useful to farmers who want to find the cheapest foods that will produce the biggest animals in the shortest time. But that kind of research climate has spread a degraded concept of nutrition into the culture at large, influencing medical ideas of nutrition, the attitudes of consumers, and the policies of governmental regulatory agencies.

When synthetic amino acids are used to supplement natural proteins, they are usually chosen according to irrelevant models of the "ideal protein's" composition, and many toxic contaminants are invariably present in the synthetic free amino acids.

For the present, the important thing is to avoid the use of the least appropriate food products, while choosing natural foods that have historical, epidemiological, and biochemical justification.

Whey has been promoted as a protein supplement, but it contains a slightly higher proportion of tryptophan than milk does. Cheese (milk with the whey removed) contains less tryptophan. Some people have been encouraged to eat only the whites of eggs, "to avoid cholesterol," but the egg albumin is rich in tryptophan.

The expensive tender cuts of meat contain excessive amounts of cysteine and tryptophan, but bone broth (gelatin) and the tougher cuts of meat contain more gelatin, which lacks those amino acids. Many fruits are deficient in tryptophan, yet have very significant quantities of the other amino acids. They also contain some of the "carbon skeleton" (keto-acid) equivalents of the essential amino acids, which can be converted to protein in the body.

Serotonin excess produces a broad range of harmful effects: Cancer, inflammation, fibrosis, neurological damage, shock, bronchoconstriction, and hypertension, for example. Increased serotonin impairs learning, serotonin antagonists improve it.

The simplest, nonessential, amino acid, glycine, has been found to protect against carcinogenesis, inflammation, fibrosis, neurological damage, shock, asthma, and hypertension. Increased glycine improves learning,[11,12] glycine antagonists usually impair it. Its antitoxic and cytoprotective actions are remarkable. Collagen, besides being free of tryptophan, contains a large amount of glycine—32 % of its amino acid units, 22 % of its weight.

The varied antiinflammatory and protective effects of glycine can be thought of as an antiserotonin action. For example, serotonin increases the formation of TNF (tumor necrosis factor, also called cachectin), glycine inhibits it. In some situations, glycine is known to suppress the formation of serotonin. Antagonists of serotonin can potentiate glycine's effects.[13] People who ate traditional diets, besides getting a lower concentration of tryptophan, were getting a large amount of glycine in their gelatin-rich diet.

Gelatin, besides being a good source of glycine, also contains a large amount of proline, which has some antiexcitatory properties similar to glycine.

If a half-pound of steak is eaten, it would probably be reasonable to have about 20 g of gelatin at approximately the same time. Even a higher ratio of gelatin to muscle meat might be preferable.

Carbon dioxide, high altitude, thyroid, progesterone, caffeine, aspirin, and decreased tryptophan consumption protect against excessive serotonin release. When sodium intake is restricted, there is a sharp increase in serotonin secretion. This accounts for some of the antiinflammatory and diuretic effects of increased sodium consumption—increasing sodium lowers both serotonin and adrenalin.

The polyunsaturated oils interact closely with serotonin and tryptophan, and the short and medium chain saturated fatty acids have antihistamine and antiserotonin actions. Serotonin liberates free fatty acids from the tissues, especially the polyunsaturated fats, and these in turn liberate serotonin from cells such as the platelets, and liberate tryptophan from serum albumin, increasing its uptake and the formation of serotonin in the brain. Saturated fats don't liberate serotonin, and some of them, such as capric acid found in coconut oil, relax blood vessels, while linoleic acid constricts blood vessels and promotes hypertension. Stress, exercise, and darkness, increase the release of free fatty acids, and so promote the liberation of tryptophan and formation of serotonin. Increased serum linoleic acid is specifically associated with serotonin-dependent disorders such as migraine.

Coconut oil, because of its saturated fatty acids of varied chain length, and its low linoleic acid content, should be considered as part of a protective diet.

In the collagen theory of aging, it is argued that changes in the extracellular matrix are responsible for isolating cells from their environment, reducing the availability of nutrients and oxygen, and reducing their ability to send and receive the chemical signals that are needed for correct adaptive functioning.

In diabetes, basement membranes are thickened, and in a given volume of tissue there are fewer capillaries. This effect probably involves excessive serotonin.[14] Old animals contain a higher proportion of collagen. Old tendons (or tendons that have been exposed to excessive estrogen, which stimulates the formation of collagen) are more rigid, and behave almost as if they have been partly cooked. In diseases such as carcinoid, in which very large amounts of serotonin are released systemically, fibrosis is exaggerated, and may be the direct cause of

death. Radiation and oxygen deprivation also lead to increased tissue fibrosis.

In specific fibrotic conditions, such as cirrhosis of the liver, it is known that glycine and saturated fats can reverse the fibrosis. In fibrosis of the heart, thyroid hormone is sometimes able to reverse the condition.

I think these facts imply that excessive tryptophan, estrogen, and polyunsaturated fats contribute significantly, maybe decisively, to the degenerative changes that occur in aging. Experiments have separately shown that reducing dietary tryptophan or unsaturated fats can extend the healthy lifespan, and several antiestrogenic interventions (removal of the pituitary, or supplementing with progesterone) can slow age-related changes and delay degenerative diseases. Since these factors interact, each tending to promote the others, and also interact with exogenous toxins, excess iron accumulation, and other stressors, it would be reasonable to expect greater results when several of the problems are corrected at the same time.

Unsaturated Fatty Acids

Nutritionally Essential, or Toxic?

Ray Peat's Newsletter, 2007

In 1929 George and Mildred Burr published a paper claiming that unsaturated fats, and specifically linoleic acid, were essential to prevent a particular disease involving dandruff, dermatitis, slowed growth, sterility, and fatal kidney degeneration.

In 1929, most of the B vitamins and essential trace minerals were unknown to nutritionists. The symptoms the Burrs saw are easily produced by deficiencies of the vitamins and minerals that they didn't know about.

What really happens to animals when the "essential fatty acids" are lacking, in an otherwise adequate diet?

- Their metabolic rate is very high.
- Their nutritional needs are increased.
- They are very resistant to many of the common causes of sickness and death.
- They are resistant to the biochemical and cellular changes seen in aging, dementia, autoimmunity, and the main types of inflammation.

The amount of polyunsaturated fatty acids often said to be essential[1] is approximately the amount required to significantly increase the incidence of cancer, and very careful food selection is needed for a diet that provides a lower amount.

When I was studying the age pigment, lipofuscin, and its formation from polyunsaturated fatty acids, I saw the 1927 study in which a fat free diet practically eliminated the development of spontaneous cancers in rats (Bernstein and Elias). I have always wondered whether George and Mildred Burr were aware of that study in 1929, when they published their claim that polyunsaturated fats are nutritionally essential. The German study was abstracted in Biological Abstracts, and the Burrs later cited several studies from German journals, and dismissively mentioned two U.S. studies[2,3] that claimed animals could live on fat-free diets, so their neglect of such an important claim is hard to understand.

Since 1927, others have demonstrated that the polyunsaturated fats are essential for the development of cancer (and some other degenerative diseases), but the Burrs' failed to even mention the issue at any time during their careers. How could they, studying fat-free diets, have missed an important contemporary publication, if I, 40 years later, saw it? There were very few publications on dietary fats in those years, so it was hardly possible to miss it.

When researchers at the Clayton Foundation Biochemical Institute at the University of Texas demonstrated that "Burr's disease" was actually a vitamin B_6 deficiency, rather than a fatty acid deficiency, the issue was settled. Later studies failed to confirm the existence of the Burr disease caused by a deficiency of fatty acids, though many similar conditions were produced by a variety of other dietary defects. In 1938, a group in Burr's own laboratory[4] failed to produce dermatitis in a man during a six-month experiment. Neither of the other major features of the Burr disease, male sterility and kidney degeneration, has been subsequently confirmed. The claim that polyunsaturated fatty acid deficiency caused sterility of male animals ("A new and uniform cause of sterility is shown") was quickly dropped, probably because an excess of polyunsaturated fats was discovered to be an important cause of testicular degeneration and sterility.

One of the features of the Burrs' rats on the fat-free diet was that they ate more calories and drank much more water than the rats that received polyunsaturated fatty acids in their diet. They believed that the animals were unable to synthesize fat without linoleic acid, although in another context they cited a study in which the fat of rats on a fat-free diet was similar in composition to lard: "McAmis, Anderson, and Mendel[5] fed rats a high sucrose, fat-free diet and rendered the fat of the entire animal. This fat had an iodine number of 64 to 71, a fairly normal value for lard."

The "wasteful" food consumption, and the leanness of animals that weren't fed polyunsaturated fats became fairly common knowledge by the late 1940s, but no one repeated the Burrs' claim that the absence of those fatty acids led quickly to the animals' death. Meanwhile, "crazy chick disease" caused by feeding an excess of polyunsaturated fats, and a little later, "yellow fat disease," caused by too much fish fat, were being recognized by farmers. In the 1950s, the seed oil industry created the anti-cholesterol diet culture, and a few decades later, without any new "Burr-like" publications, the omega minus 3 oils, especially fish oils, were

coming to be represented as the overlooked essential fatty acids, which were capable of preventing the toxic effects of the original "essential" linoleic acid.

Although the 1929 Burr paper is still often cited as proof of the essentiality of PUFA, Burr's younger colleague (at the University of Minnesota Hormel Institute), Ralph Holman, has cited an infant (1970), and a 78 year old woman (in 1969), who developed dermatitis while receiving fat-free intravenous feedings. Dermatitis, with dandruff, similar to Burr's disease, has been produced by various nutritional deficiencies besides vitamin B_6, including a trace mineral deficiency and a biotin deficiency, so there is no valid reason to associate dermatitis with a fat deficiency. The cases of "EFA deficiency" produced by intravenous feedings that have been widely cited were probably the result of a deficiency of zinc or other trace mineral, since so-called "Total Parenteral Nutrition" was in use for many years before the trace minerals were added to the "total" formula. In 1975, I learned that our local hospital was putting all premature babies on what they called total intravenous feeding, without trace minerals, for weeks, or months. There is still more emphasis on polyunsaturated fat in intravenous feeding than on the essential trace nutrients.

Holman and the Hormel Institute have been extremely influential in promoting the doctrine of the essentiality of PUFA, including fish oils and the omega -3 oils, but their best evidence, the Burr experiment, doesn't make their case. Far worse than that is the effect it has had in distracting attention from the profoundly toxic effects of the so-called essential fatty acids. Long after he should have known better, Holman was arguing that butter was a nutritionally inferior fat.

When the Burrs were doing their study, Raymond Pearl was one of the most famous biologists in the country, and his "rate of living" theory of aging was very widely known. According to that theory, an organism has an intrinsic potential to produce a certain total amount of energy during its lifetime, and if it metabolizes at a higher than normal rate, its life span will be proportionately shorter than normal.

There is general agreement that animals on a fat free diet have a very high metabolic rate, but the people who believe the "rate of living" theory will be inclined to see the increased rate of metabolism as something harmful in itself. It is clear that this is what the Burrs thought. They

didn't attempt to provide a diet that provided increased amounts of all vitamins and minerals, in proportion to the increased metabolic rate.

Pearl did an experiment, sprouting cantaloupe seeds in a dish with water. The sprouts that grew rapidly died sooner than those that grew more slowly. They died as soon as the nutrients stored in the endosperm had been consumed. Naturally, when nutrients are depleted, growth and metabolism must stop. If food and air and water are rationed, then slow metabolizers are going to live longer. But when nutritional needs are met, the organisms with the highest metabolic rate generally are healthier and live longer. In a study of nurses, those who habitually consumed the most calories lived longer than those who consumed the least. Even while Pearl was promoting his theory, other famous biologists, for example John Northrup in Jacques Loeb's lab at the Rockefeller Institute, were making observations that contradicted the rate of living theory. For example, around 1916, Northrup observed that fruit flies that metabolized at the highest rate lived the longest. Northrup was doing biology, Pearl was doing propaganda, following Weismannism.

The idea of extending life span by slowing metabolism and growth was a logical implication of the "rate of living" theory of aging, and it's an idea that is still popular. Many people have supposed that eating less would slow metabolism. Caloric restriction does extend the life span of many species, but it generally preserves the high metabolic rate of youth, so that at a given age the calorie-restricted animal has a higher rate of oxygen consumption per gram of body weight than the unrestricted eaters.

Roy Walford, a gerontologist who wrote about extending the human life span to 120 years by caloric restriction, spent 30 years limiting his diet to about 1600 calories, with little animal protein, almost no saturated fat—fish once or twice per week, poultry or beef about once, and a fat free milkshake for breakfast—and after about 15 years, began developing a degenerative brain disease, ALS, one of the nerve diseases involving lipid peroxidation and excitotoxicity. When he died from the disease, he had lived a year longer than the normal life expectancy.

V. Stefannson, one of the early polar explorers, spent a winter living entirely on caribou meat, and felt that it had prevented the scurvy that had killed so many of the other explorers, who had counted on fruit and vegetables to prevent it. But he believed that meat was a metabolic stimulant that made people age prematurely, as Pearl's rate of living

theory predicted. Stefannson said that Eskimo women were getting old in their twenties, and that at the age of 60 they looked as old as Europeans did at 80. He was a well informed anthropologist, and his observations were probably accurate. The Eskimos he observed ate large amounts of fish, and other unsaturated fats, and sometimes ate highly decayed fish. An accelerated rate of aging would be expected from such a diet, because of the toxic lipid peroxides.

Calorie-restricted animals (on a diet of normal composition) have a lower degree of fat unsaturation in their mitochondria as they age, preserving the relatively more saturated fats of youth.

Birds' mitochondrial fats are much less polyunsaturated than those of mammals, and birds' metabolic rates are much higher, and they live much longer than mammals of a similar size.

With aging, the highly peroxidizable fatty acids, arachidonic and docosahexaenoic acid, increase greatly in a variety of tissues, and lipid peroxidation increases with aging. Peroxidation slows mitochondrial respiration, lowering the metabolic rate. Caloric restriction slows the accumulation of the highly unsaturated fatty acids in mitochondria, and reduces peroxidation.

Over the years, it has become evident that the polyunsaturated fats are not very compatible with a high rate of metabolism, though they are necessary for organisms that live at low temperatures and metabolize slowly, such as fish and vegetables. The saturated fats solidify at low temperature; beef fat is very stiff at refrigerator temperature, and in a fat fish, such stiffness would be lethal.

Even some hibernating rodents can stay alive with their body tissues close to the freezing point, and their stored fats have to be unsaturated. When their diet doesn't allow them to store enough polyunsaturated fat, they fail to go into hibernation. This is probably a clue to some of the general biological effects of the PUFA.

A series of studies about 20 years ago showed that the functions of the thyroid hormone are all inhibited by unsaturated fats, with the inhibition increasing in proportion to the number of unsaturations (double bonds) in the fat molecule.

When the tissues are saturated with those antithyroid fats, metabolism slows, especially when any stress, such as cold or hunger, increases the concentration of free fatty acids in the blood stream. Stress and hypothyroidism increase the formation of serotonin, which is an

important factor in producing the torpor of hibernation, and lowering the body temperature. The polyunsaturated fatty acids themselves directly contribute to the formation of serotonin, for example by increasing the ability of tryptophan to enter the brain. In a certain cold climate, the PUFA are essential for hibernation, but under other conditions, the rodent would be able to continue gathering food and eating, instead of hibernating.

The direct effects of the PUFA on the endocrine and nervous systems, as illustrated by the hibernating squirrel, interact with their effects on intercellular communication (including the formation of prostaglandins and related substances), and the effects of their oxidative breakdown products, such as acrolein. But the people who claim that they are absolutely, rather than conditionally, essential, base their argument on the idea that they are needed for the formation of prostaglandins and cell membranes. The fact that cells can replicate in fat free conditions shows that the argument from membranes is unfounded. The argument from prostaglandins is more complex, but has no firmer foundation.

When a dose of PUFA is administered to a lizard, which isn't a hibernator, the lizard's body temperature is lowered by several degrees. There are probably many ways in which the PUFA produce that effect, besides increasing serotonin and decreasing thyroid. The PUFA are increased by estrogen, and they increase estrogen, and have some directly estrogen-like effects. Estrogen itself tends to lower body temperature and shift metabolism away from oxidative energy production. Aging, like estrogen, increases the body's content of the PUFA: Linoleic, linolenic, dihomo-gamma-linolenic, docosahexaenoic and docosapentaenoic acids are increased by age, and the longer chain acids increase more rapidly in women than in men.[6] (Women are apparently relatively protected by progesterone, which inhibits lipolysis and prostaglandin formation, and protects the brain, thymus, and other tissues from lipid peroxidation and other effects of the PUFA.)

Aging involves a decreasing metabolic rate, an increased tendency toward inflammation, and a decreased ability to synthesize proteins. Inflammation contributes to the decreasing ability to use oxygen, and the slowed renewal of proteins combined with lower ability to produce energy impair the organism's ability to control peroxidative damage and inflammation.

The fragments of deteriorating PUFA combine with proteins and other cell materials, producing immunogenic substances. The so-called "advanced glycation end products," that have been blamed on glucose excess, are mostly derived from the peroxidation of the "essential fatty acids." The name, "glycation," indicates the addition of sugar groups to proteins, such as occurs in diabetes and old age, but when tested in a controlled experiment, lipid peroxidation of polyunsaturated fatty acids produces the protein damage about 23 times faster than the simple sugars do.[7]

Several autoimmune disease models in animals (involving the eye, kidney, and pancreas) have been prevented by a deficiency of the EFA.[8–10]

Besides causing a general slowing of metabolism, aging and toxic PUFA have specific actions on the detoxifying system. The enzymes that help to detoxify PUFA and estrogen and serotonin are inhibited by both PUFA and estrogen. All systems, including blood vessels and the intestine, are made leaky by estrogen and the PUFA and their products. A reduced ability to regulate the excitatory amino acids, resulting from PUFA toxins, tends to produce excitotoxicity, damaging nerves.[11]

Although the interplay of the various types of nerve is very complex, a variety of experiments suggest that the PUFA are acting directly on serotonergic nerves, rather than just increasing the conversion of tryptophan to serotonin.

For example, a deficiency of the so-called essential fatty acids, EFA, makes animals more sensitive to some anesthetics, and more resistant to others. It makes them resistant to the anesthetics that act by promoting the actions of serotonin, but it prolongs the effects of those that don't act through serotonin, and these are the anesthetics such as xenon and nitrous oxide, that apparently act by stabilizing the structure of water, as described by Linus Pauling. Progesterone and the saturated fats seem to act partly through the stabilizing of cell water, and estrogen and the PUFA have opposing effects, creating cellular excitation while interfering with the stable cellular water structure.

Serotonin interferes with slow wave sleep, and promotes cortisol, both of which can be harmful to brain cells. (Hypothyroidism is one of the causes of a decrease in slow wave sleep.) Babies whose mothers' serum contained more DHA were more wakeful on their second day of life, than the babies of low-DHA mothers. The amide of oleic acid

is a sleep promoter, with apparent antiserotonin activity,[12] and since oleic acid tends to be displaced by diets high in PUFA, this suggests another way in which the highly unsaturated fatty acids could promote serotonin's effects.

People who don't have a normal amount of slow wave sleep are likely to have slow reaction times when they are awake, and quickness of reactions is a good indicator of general intelligence.

Manufacturers of baby formulas are claiming that the highly unsaturated fatty acids accelerate brain development, but they neglect to mention studies that show either no effect, or retardation of development. In some of the tests that are used to measure infant development, a generalized state of arousal or anxiety could be interpreted as "more mature."

In one experiment, animals that received less than 0.32 % of their calories as EFA grew slightly less than rats on a standard diet, but their brains were as large as those of normal rats.[13] That is, their brain to body ratio was a little larger than normal, which is a typical feature of individuals with a higher metabolic rate. That result is very different from the claims of the baby food industry, that the brain is the organ most easily damaged by a PUFA deficiency.

One of the standard signs of toxicity is the enlargement of the spleen and liver, and that effect is produced by larger amounts of the EFA. The weight of the thymus is reduced by PUFA in the diet.[14] Thymus cells tend to be easily killed by a combination of stress and EFA, and bone marrow cells, though less sensitive than thymic cells, are damaged by lipid peroxidation of the PUFA. The effects of PUFA on the thymus were compared to those of radiation by Soviet researchers. Immunodeficiency, produced largely by damage to thymic cells, increases when larger amounts of PUFA are eaten for a prolonged time.

The growth and metastasis of a variety of tumors are inhibited by saturated fatty acids, and increased by fish oil—as much as 10 times in number of metastases, 1000 times in size.[15]

Mothers whose breast milk contains more long-chain n-3 fatty acids are more likely to have allergic children.[16] (And children whose mothers are allergic have higher levels of DHA and EPA in their tissues.) These associations aren't mentioned by the manufacturers who speak of those fats as essential.

When animals have been "deprived" of the EFA during gestation and nursing, and then given a standard diet, they develop larger bones, with a thicker cortex and more trabecular bone, both of which would suggest a lower level of stress. Many types of inflammation and stress are significantly reduced in "EFA deficient" animals. Inflammation caused by the injection of carrageenan is decreased, partly because of the absence of prostaglandins in these animals. The absence of the EFA protects against colitis and nephritis. The kidneys are more effective in several ways in the deficient animals.

Shock, caused by the injection of endotoxin, which is 100 % lethal to normally fed animals, is only 24 % lethal to the deficient animals.

Poisons are much less harmful to deficient animals, for example, a cobra venom factor causes less tissue damage to their lungs.

Concussive trauma and burns cause much less damage to deficient animals.

The endothelial lining of blood vessels is protected by saturated fats and oleic acid, damaged by polyunsaturated, and their barrier function is improved by the absence of PUFA.

Alzheimer's disease, retinal degeneration, cataracts, and liver cirrhosis all involve reactions of oxidized PUFA with proteins. Saturated fats help to heal alcoholic liver cirrhosis.

The lesions of atherosclerosis and cataracts contain some of the same oxidized lipids as the age pigment itself. When large deposits of age pigment become visible, it's probably because the general reduction of metabolism and protein synthesis has interfered with the normal processes for removing debris. The age pigment contributes to degeneration by wasting energy and oxygen, weakening the antioxidation, antiglycation, and other defensive systems.

The EFA amplify nearly all kinds of injury and stress, and the results of many recent publications make it look as though serotonin interacts harmfully with the EFA in most of these situations. The specific balance of polyunsaturated fatty acids, and their various breakdown products, from carbon monoxide, glyoxal, and acrolein, to the larger aldehydes and radicals, and the stress-induced substances such as serotonin, histamine, estrogens, can produce an immense variety of biological problems.

When the various claims of an EFA "deficiency disease" or syndrome or symptom are examined, their inconsistency over the years makes skepticism seem increasingly justified. The Burrs' publications were

typical of others, in failing to describe and account for the evidence that contradicted their claims. Claiming that certain fatty acids are essential, a scientific approach would require showing what was wrong with the experiments that showed that they were not essential, and especially, those that showed that they were positively harmful.

In this culture that repeatedly makes such claims of essentiality, the growing number of reports of biological superiority of "deficient" animals suggests that nutritional research may be near the point at which it can resume the line of study begun by Northrup, Osborne, Mendel, Drummond, Bernstein, Elias, and others, that was interrupted for 60 years by industrial interests that promoted antiscientific opinions.

For example, in 1914 F. P. Rous showed that limiting food intake reduced the incidence of cancer, and then in 1915 and 1917, Osborne and Mendel showed that food restriction extended the fertility and longevity of female rats. The association between estrogen and cancer had become known during this time, and vitamin E, which was originally known as the fertility vitamin, was soon recognized to have antiestrogenic properties, as well as to prevent the deadly effects of excessive polyunsaturated fats in the diet. My endocrinology professor, A. S. Soderwall, who had found that excess estrogen prevented (or interrupted) pregnancy, demonstrated that increased vitamin E extended fertility in aging female rodents.

By the time I began my research, it seemed clear that it had been the reduction of PUFA in the diet which, like the addition of vitamin E, had prevented sterility in the calorie restriction experiments, and that those treatments had limited the effects of estrogen in the aging organisms.

Estrogen, by activating phospholipase A_2, acts to amplify the toxic effects of PUFA in the tissues, and these effects increase with age, and with decreased amounts of thyroid and progesterone.

Antioxidants can slightly retard the cumulative degenerative effects of the fats interacting with estrogen, serotonin, and other mediators of inflammation, but real elimination of the degenerative diseases will require an exploration of the effects of the entire series of lipid signalling substances derived from the saturated and omega minus 9 fatty acids.

Unsaturated Vegetable Oils: Toxic

Ray Peat's Newsletter, 2006

IMMUNODEFICIENCY (weakness of the immune system) can take many forms. AIDS, for example, refers to an immunodeficiency which is "acquired," rather than "inborn." Radiation and vegetable oils can cause "acquired immunodeficiency." Unsaturated oils, especially polyunsaturates, weaken the immune system's function in ways that are similar to the damage caused by radiation, hormone imbalance, cancer, aging, or viral infections. The media discuss sexually transmitted and drug-induced immunodeficiency, but it isn't yet considered polite to discuss vegetable oil-induced immunodeficiency.

Unsaturated oils: When an oil is saturated, that means that the molecule has all the hydrogen atoms it can hold. Unsaturation means that some hydrogen atoms have been removed, and this opens the structure of the molecule in a way that makes it susceptible to attack by free radicals.

Free radicals are reactive molecular fragments that occur even in healthy cells, and can damage the cell. When unsaturated oils are exposed to free radicals they can create chain reactions of free radicals that spread the damage in the cell, and contribute to the cell's aging.

Rancidity of oils occurs when they are exposed to oxygen, in the body just as in the bottle. Harmful free radicals are formed, and oxygen is used up.

Essential fatty acids (EFA) are, according to the textbooks, linoleic acid and linolenic acid, and they are supposed to have the status of "vitamins," which must be taken in the diet to make life possible. However, we are able to synthesize our own unsaturated fats when we don't eat the "EFA," so they are not "essential." The term thus appears to be a misnomer.[1]

Q: You say vegetable oils are hazardous to your health. What vegetable oils are you talking about?

Mainly, I'm referring to soybean oil, corn oil, safflower oil, canola, sesame oil, sunflower seed oil, palm oil, and any others that are labeled

as "unsaturated" or "polyunsaturated." Almond oil, which is used in many cosmetics, is very unsaturated.

Chemically, the material that makes these oils very toxic is the polyunsaturated fat itself. These unsaturated oils are found in very high concentrations in many seeds, and in the fats of animals that have eaten a diet containing them. The fresh oils, whether cold pressed or consumed as part of the living plant material, are intrinsically toxic, and it is not any special industrial treatment that makes them toxic. Since these oils occur in other parts of plants at lower concentration, and in the animals which eat the plants, it is impossible to eat a diet which lacks them, unless special foods are prepared in the laboratory.

These toxic oils are sometimes called the "essential fatty acids" or "vitamin F," but this concept of the oils as essential nutrients was clearly disproved over 50 years ago.

Linoleic and linolenic acids, the "essential fatty acids," and other polyunsaturated fatty acids, which are now fed to pigs to fatten them, in the form of corn and soy beans, cause the animals' fat to be chemically equivalent to vegetable oil. In the late 1940s, chemical toxins were used to suppress the thyroid function of pigs, to make them get fatter while consuming less food. When that was found to be carcinogenic, it was then found that corn and soy beans had the same antithyroid effect, causing the animals to be fattened at low cost. The animals' fat becomes chemically similar to the fats in their food, causing it to be equally toxic, and equally fattening.

These oils are derived from seeds, but their abundance in some meat has led to a lot of confusion about "animal fats." Many researchers still refer to lard as a "saturated fat," but this is simply incorrect when pigs are fed soybeans and corn.

Q: How are these oils hazardous to your health?

Ultimately, all systems of the body are harmed by an excess of these oils. There are two reasons for this. One is that the plants produce the oils for protection, not only to store energy for the germination of the seed. To defend the seeds from the animals that would eat them, the oils block the digestive enzymes in the animals' stomachs. Digestion is one of our most basic functions, and evolution has built many other systems

by using variations of that system; as a result, all of these systems are damaged by the substances which damage the digestive system.

The other reason is that the seeds are designed to germinate in early spring, so their energy stores must be accessible when the temperatures are cool, and they normally don't have to remain viable through the hot summer months. Unsaturated oils are liquid when they are cold, and this is necessary for any organism that lives at low temperatures. For example, fish in cold water would be stiff if they contained saturated fats. These oils easily get rancid (spontaneously oxidizing) when they are warm and exposed to oxygen. Seeds contain a small amount of vitamin E to delay rancidity. When the oils are stored in our tissues, they are much warmer, and more directly exposed to oxygen, than they would be in the seeds, and so their tendency to oxidize is very great. These oxidative processes can damage enzymes and other parts of cells, and especially their ability to produce energy.

The enzymes which break down proteins are inhibited by unsaturated fats, and these enzymes are needed not only for digestion, but also for production of thyroid hormones, clot removal, immunity, and the general adaptability of cells. The risks of abnormal blood clotting, inflammation, immune deficiency, shock, aging, obesity, and cancer are increased. Thyroid and progesterone are decreased. Since the unsaturated oils block protein digestion in the stomach, we can be malnourished even while "eating well."

Plants produce many protective substances to repel or injure insects and other animals that eat them. They produce their own pesticides. The oils in seeds have this function. On top of this natural toxicity, the plants are sprayed with industrial pesticides, which can concentrate in the seed oils.

It isn't the quantity of these polyunsaturated oils which governs the harm they do, but the relationship between them and the saturated fats. Obesity, free radical production, the formation of age pigment, blood clotting, inflammation, immunity, and energy production are all responsive to the ratio of unsaturated fats to saturated fats, and the higher this ratio is, the greater the probability of harm there is.

There are interesting interactions between these oils and estrogen. For example, puberty occurs at an earlier age if estrogen is high, or if these oils are more abundant in the diet. This is probably a factor in the development of cancer.

All systems of the body are harmed by an excess of these oils. There are three main kinds of damage: one, hormonal imbalances, two, damage to the immune system, and three, oxidative damage.

Q: How do they cause hormonal imbalances?

There are many changes in hormones caused by unsaturated fats. Their best understood effect is their interference with the function of the thyroid gland. Unsaturated oils block thyroid hormone secretion, its movement in the circulatory system, and the response of tissues to the hormone. When the thyroid hormone is deficient, the body is generally exposed to increased levels of estrogen. The thyroid hormone is essential for making the "protective hormones" progesterone and pregnenolone, so these hormones are lowered when anything interferes with the function of the thyroid. The thyroid hormone is required for using and eliminating cholesterol, so cholesterol is likely to be raised by anything which blocks the thyroid function. (B. Barnes and L. Galton, Hypothyroidism, 1976, and 1994 references.)

Q: How do they damage the immune system?

Vegetable oil is recognized as a drug for knocking out the immune system. Vegetable oil emulsions were used to nourish cancer patients, but it was discovered that the unsaturated oils were suppressing their immune systems. The same products, in which vegetable oil is emulsified with water for intravenous injection, are now marketed specifically for the purpose of suppressing immunity in patients who have had organ transplants. Using the oils in foods has the same harmful effect on the immune system.[2] Unsaturated fats directly kill white blood cells.[3]

Q: How do they cause oxidative damage?

Unsaturated oils get rancid when exposed to air; that is called oxidation, and it is the same process that occurs when oil paint "dries." Free radicals are produced in the process.

This process is accelerated at higher temperatures. The free radicals produced in this process react with parts of cells, such as molecules of

DNA and protein and may become attached to those molecules, causing abnormalities of structure and function.

Q: What if I eat only organically grown vegetable oils?

Even without the addition of agricultural chemicals, an excess of unsaturated vegetable oils damages the human body. Cancer can't occur, unless there are unsaturated oils in the diet.[4] Alcoholic cirrhosis of the liver cannot occur unless there are unsaturated oils in the diet.[5] Heart disease can be produced by unsaturated oils, and prevented by adding saturated oils to the diet.[6]

Q: What oils are safe?

Coconut and olive oil are the only vegetable oils that are really safe, but butter and lamb fat, which are highly saturated, are generally very safe (except when the animals have been poisoned). Coconut oil is unique in its ability to prevent weight-gain or cure obesity, by stimulating metabolism. It is quickly metabolized, and functions in some ways as an antioxidant. Olive oil, though it is somewhat fattening, is less fattening than corn or soy oil, and contains an antioxidant which makes it protective against heart disease and cancer.

Israel had the world's highest incidence of breast cancer when they allowed the insecticide lindane to be used in dairies, and the cancer rate decreased immediately after the government prohibited its use. The United States has fairly good laws to control the use of cancer-causing agents in the food supply, but they are not vigorously enforced. Certain cancers are several times more common among corn farmers than among other farmers, presumably because corn "requires" the use of more pesticides. This probably makes corn oil's toxicity greater than it would be otherwise, but even the pure, organically grown material is toxic, because of its intrinsic unsaturation.

In the United States, lard is toxic because the pigs are fed large quantities of corn and soy beans. Besides the intrinsic toxicity of the seed oils, they are contaminated with agricultural chemicals. Corn

farmers have a very high incidence of cancer, presumably because of the pesticides they use on their crop.

Q: But aren't "tropical oils" bad for us?

In general, tropical oils are much more healthful than oils produced in a cold climate. This is because tropical plants live at a temperature that is close to our natural body temperature. Tropical oils are stable at high temperatures. When we eat tropical oils, they don't get rancid in our tissues as the cold-climate seed oils, such as corn oil, safflower oil and soy oil, do.[7,8]

When added to a balanced diet, coconut oil slightly lowers the cholesterol level, which is exactly what is expected when a dietary change raises thyroid function. This same increase in thyroid function and metabolic rate explains why people and animals that regularly eat coconut oil are lean, and remarkably free of heart disease and cancer.

Although I don't recommend "palm oil" as a food, because I think it is less stable than coconut oil, some studies show that it contains valuable nutrients. For example, it contains antioxidants similar to vitamin E, which lowers both LDL cholesterol and a platelet clotting factor. (B. A. Bradlow, University of Illinois, Chicago; Science News 139, 268, 1991.) Coconut oil and other tropical oils also contain some hormones that are related to pregnenolone or progesterone.

Q: Isn't coconut oil fattening?

Coconut oil is the least fattening of all the oils. Pig farmers tried to use it to fatten their animals, but when it was added to the animal feed, coconut oil made the pigs lean (See *Encyclopaedia Britannica Book of the Year*, 1946).

Q: What about olive oil? Isn't it more fattening than other vegetable oils?

In this case, as with coconut oil, "fattening" has more to do with your ability to burn calories than with the caloric value of the oil. Olive oil has a few more calories per quart than corn or soy oil, but since it doesn't damage our ability to burn calories as much as the unsaturated oils do, it is less fattening. Extra virgin olive oil is the best grade, and

contains an antioxidant that protects against cancer and heart disease. (1994, Curr. Conts.)

Q: Is "light" olive oil okay?

No. Now and then someone learns how to make a profit from waste material. "Knotty pine" boards were changed from a discarded material to a valued decorative material by a little marketing skill. Light olive oil is a low grade material which sometimes has a rancid smell and probably shouldn't be used as food.

Q: Is margarine okay?

There are several problems with margarine. The manufacturing process introduces some toxins, including a unique type of fat which has been associated with heart disease. (Sci. News, 1974; 1991.) There are likely to be dyes and preservatives added to margarine. And newer products contain new chemicals that haven't been in use long enough to know whether they are safe.

However, the basic hardening process, hydrogenation of the oils, has been found to make the oils less likely to cause cancer. If I had to choose between eating ordinary corn oil or corn oil that was 100% saturated, to make a hard margarine, I would choose the hard margarine, because it resists oxidation, isn't suppressive to the thyroid gland, and doesn't cause cancer.

Q: What about butter?

Butter contains natural vitamin A and D and some beneficial natural hormones. It is less fattening than the unsaturated oils. There is much less cholesterol in an ounce of butter than in a lean chicken breast (about 1/5 as much cholesterol in fat as in lean meat on a calorie basis, according to R. Reiser of Texas A & M Univ., 1979.).

Q: Are fish oils good for you?

Some of the unsaturated fats in fish are definitely less toxic than those in corn oil or soy oil, but that doesn't mean they are safe. Fifty

years ago, it was found that a large amount of cod liver oil in dogs' diet increased their death rate from cancer by 20 times, from the usual 5 % to 100 %. A diet rich in fish oil causes intense production of toxic lipid peroxides, and has been observed to reduce a man's sperm count to zero. (H. Sinclair, Prog. Lipid Res. 25, 667, 1989.)

Q: What about lard?

In this country, lard is toxic because the pigs are fed large quantities of corn and soy beans. Besides the natural toxicity of the seed oils, the oils are contaminated with agricultural chemicals. Corn farmers have a very high incidence of cancer, presumably because corn "requires" the use of more pesticides. This probably makes corn oil's toxicity greater than it would be otherwise. but even the pure, organically grown material is toxic, because of its unsaturation.

Women with breast cancer have very high levels of agricultural pesticides in their breasts (See Science News, 1992, 1994).

Israel had the world's highest incidence of breast cancer when they allowed the insecticide lindane to be used in dairies, and the cancer rate decreased immediately after the government prohibited its use. The United States has fairly good laws to control the use of cancer-causing agents in the food supply, but they are not vigorously enforced. (World Incid. of Cancer, 1992)

Q: I have no control over oils when eating out. What can I do to offset the harmful effects of polyunsaturated oils?

A small amount of these oils won't kill you. It is the proportion of them in your diet that matters. A little extra vitamin E (such as 100 units per day) will take care of an occasional American restaurant meal. Based on animal studies, it would take a teaspoonful per day of corn or soy oil added to a fat-free diet to significantly increase our risk of cancer. Unfortunately, it is impossible to devise a fat-free diet outside of a laboratory. Vegetables, grains, nuts, fish and meats all naturally

contain large amounts of these oils, and the extra oil used in cooking becomes a more serious problem.

Q: Why are the unsaturated oils so popular if they are dangerous?

It's a whole system of promotion, advertising, and profitability. 50 years ago, paints and varnishes were made of soy oil, safflower oil, and linseed (flax seed) oil. Then chemists learned how to make paint from petroleum, which was much cheaper. As a result, the huge seed oil industry found its crop increasingly hard to sell. Around the same time, farmers were experimenting with poisons to make their pigs get fatter with less food, and they discovered that corn and soy beans served the purpose, in a legal way. The crops that had been grown for the paint industry came to be used for animal food. Then these foods that made animals get fat cheaply came to be promoted as foods for humans, but they had to direct attention away from the fact that they are very fattening. The "cholesterol" focus was just one of the marketing tools used by the oil industry. Unfortunately it is the one that has lasted the longest, even after the unsaturated oils were proven to cause heart disease as well as cancer.[9]

I use some of these oils (walnut oil is very nice, but safflower oil is cheaper) for oil painting, but I am careful to wash my hands thoroughly after I touch them, because they can be absorbed through the skin.

Summary

- Unsaturated fats cause aging, clotting, inflammation, cancer, and weight gain.
- Avoid foods which contain the polyunsaturated oils, such as corn, soy, safflower, flax, cottonseed, canola, peanut, and sesame oil.
- Mayonnaise, pastries, even candies may contain these oils; check the labels for ingredients.
- Pork is now fed corn and soy beans, so lard is usually as toxic as those oils; use only lean pork.
- Fish oils are usually highly unsaturated; "dry" types of fish, and shellfish, used once or twice a week, are good. Avoid cod liver oil.
- Use vitamin E.
- Use coconut oil, butter, and olive oil.

- Unsaturated fats intensify estrogen's harmful effects.

Vegetables, etc.---Who Defines Food?

Ray Peat's Newsletter, 2006

Not long ago, breast feeding was socially unacceptable in the United States, and several manufacturers were teaching the world's poorest women to use their baby-food formulas even when there was no clean water for its preparation. Industrialists have campaigned to convince the public that their by-products, from cotton-seed oil to shrimp shells, are "health foods." In several parts of the world, desperately poor people sometimes eat clay, and even clay has been promoted as a health food. Almost anything becomes "food," when people are under economic and social pressure. If these things aren't acutely toxic, they can become part of our "normal" diet.

Our instincts give us a few clues about our nutritional needs, such as thirst, the hunger for salt, the pleasantness of sweet things, and the unpleasantness of certain odors or very acrid or bitter tastes. People who are constitutionally unable to taste certain bitter chemicals find certain vegetables less objectionable; their instinctive guidance has become less clear. But within the boundaries of cravings and disgust, habits and customs become the dominant forces in diet. "Professional dietitians" and other "experts" primarily function as enforcers of cultural prejudice.

The manufacturers of pureed vegetables for babies used to put large amounts of salt, sugar, and monosodium glutamate into their products, because the added chemicals served as instinctual signals that made the material somewhat acceptable to the babies. There was no scientific basis for providing these vegetables to babies in a form that they would accept, but it was a profitable practice that was compatible with the social pressure against prolonged breast feeding.

Poor people, especially in the spring when other foods were scarce, have sometimes subsisted on foliage such as collard and poke greens, usually made more palatable by cooking them with flavorings, such as

Since bacteria in the rumens of cows destroy unsaturated fatty acids, but don't harm vitamin E, it seems reasonable to suppose that beef and milk would have a better ratio of vitamin E to unsaturated fats than do the plants eaten by the cows.

Toxic pesticides are found in higher concentrations in the urine and fat of slaughtered animals than in their livers, since the livers are detoxifying the chemicals and causing them to be excreted. Presumably, the animals' livers will perform the same detoxification reactions with the phytotoxicants that occur naturally in their diet.

a little bacon grease and lots of salt. Eventually, "famine foods" can be accepted as dietary staples. The fact that cows, sheep, goats and deer can thrive on a diet of foliage shows that leaves contain essential nutrients. Their minerals, vitamins, and amino acids are suitable for sustaining most animal life, if a sufficient quantity is eaten. But when people try to live primarily on foliage, as in famines, they soon suffer from a great variety of diseases. Various leaves contain antimetabolic substances that prevent the assimilation of the nutrients, and only very specifically adapted digestive systems (or technologies) can overcome those toxic effects.

Some plants have specific "pests," such as insects, that have adapted to be resistant to that plant's toxins, but if the plant and its predator are to survive, there has to be a balance between the plant tissue's digestibility and its toxicity. Injury of a plant stimulates it to make increased amounts of its defensive chemicals. Plant toxins are known to be specific for animal tissues; for example, a toxin will inhibit the action of an enzyme from an animal, but a plant enzyme that catalyzes the same reaction won't be affected.

Plant defensive chemicals can have beneficial uses as drugs. Plants are important sources for chemicals used in chemotherapy of cancer, with the purpose of stopping cell division. Other plant drugs can stimulate cell division. The drug from one plant will sometimes protect cells against the toxic effects of another plant. The use of any drug that isn't a natural part of animal physiology will have many biological effects, so that a beneficial drug action will usually be accompanied by unwanted side-effects. An antioxidant may turn out to disrupt the endocrine system, an antiinflammatory drug may be mutagenic or carcinogenic.

A particular plant will have a variety of defensive chemicals, with specific functions. Underground, the plant's roots and tubers are susceptible to attack by fungi and nematodes. The leaves, stems, and seeds are susceptible to attack by insects, birds, and grazing animals. Since the plant's seeds are of unique importance to the plant, and contain a high concentration of nutrients, they must have special protection. Sometimes this consists of a hard shell, and sometimes of chemicals that inhibit the animal's digestive enzymes. Many plants have evolved fruits that provide concentrated food for animals, and that serve to distribute the seeds widely, as when a bird eats a berry, and excretes the undigested seed at a great distance. If the fruit were poisonous, it wouldn't serve the

plant's purpose so well. In general, the plant's most intense toxins are in its seeds, and the fruits, when mature, generally contain practically no toxins. Roots contain chemicals that inhibit microorganisms, but because they aren't easily accessible by grazing animals and insects, they don't contain the digestive inhibitors that are more concentrated in the above-ground organs of the plant.

The toxins of plants include phenols, tannins, lectins/agglutinins, and trypsin-inhibitors, besides innumerable more specific metabolic inhibitors, including "anti-vitamins." Unsaturated fats themselves are important defenses, since they inhibit trypsin and other proteolytic enzymes, preventing the assimilation of the proteins that are present in seeds and leaves, and disrupting all biological processes that depend on protein breakdown, such as the formation of thyroid hormone and the removal of blood clots.

Generally, fruits, roots, and tubers provide a high concentration of nutrients along with low concentrations of toxic antimetabolic substances.

While nutritional reference tables often show fruits and potatoes as having about 2 % protein content, while nuts, grains, and legumes are shown with a high protein content, often in the range of 15 % to 40 %, they neglect to point out that fruits and potatoes have a very high water content, while that of the seeds is extremely low. The protein content of milk is about 3 %, which according to the charts would suggest that it is inferior to beans and grains. In fact, the protein value of grain is negligible, mainly because seeds contain their protein in a storage form, that is extremely rich in nitrogen, but poor in essential amino acids. Special preparation is needed to reduce the toxicity of seeds, and in the case of beans, these methods are never very satisfactory.

Besides their specific defensive toxins and antimetabolites, plants are major sources of allergens. The allergenicity of a food depends on the sensitivity of the individual, as well as on the growth conditions of the plant. The use of extremely toxic pesticides has affected both the crops and the sensitivity of the human population to allergens. Sensitivities induced originally by toxic pesticides used on certain crops can probably persist after the industrial chemical has been eliminated, because the immune system is susceptible to "conditioning."

Many types of phytochemicals are mutagenic, and some of those are carcinogenic. Bruce Ames, at the University of California, devised

a method of screening for mutagens, using bacteria. One of his graduate students using the technique found that the flame retardants in children's pajamas and bedding were powerful mutagens, and were probably causing cancer. That event made Ames a celebrity, and in the 1980s he went on a lecture tour supported by the American Cancer Society. His lectures reflected the doctrine of the A.C.S., that industrial chemicals aren't responsible for cancer, but that individual actions, such as smoking or dietary choices, are the main causes of cancer. He used a fraudulently "age adjusted" graph of cancer mortality, that falsely showed that mortality from all types of cancer except lung cancer had leveled off after the A.C.S. came into existence. He described tests in which he had compared DDT to extracts of food herbs, and found DDT to be less mutagenic than several of the most commonly used flavoring herbs. His message, which was eagerly received by his audience of chemistry and biology professors, was that we should not worry about environmental pollution, because it's not as harmful as the things that we do to ourselves. He said that if everyone would eat more unsaturated vegetable oil, and didn't smoke, they wouldn't have anything to worry about.

For me, the significance of his experiment was that plants contain natural pesticides that should be taken more seriously, without taking industrial toxins less seriously.

Technologies have been invented to convert vegetation into digestible protein, but at our present scientific and technological level, it's better to simply minimize our use of the more toxic foods, and to direct more effort toward the elimination of the conditions that produce famine.

Animal proteins, and fruits, because they contain the lowest levels of toxins, should form the basis of the diet. Not all fruits, of course, are perfectly safe—avocados, for example, contain so much unsaturated fat that they can be carcinogenic and hepatotoxic.

Protein deficiency itself contributes to the harm done by toxins, since the liver's ability to detoxify them depends on adequate nutrition, especially good protein. In the 1940s, Biskind's experiments showed that protein deficiency leads to the accumulation of estrogen, because the liver normally inactivates all the estrogen in the blood as it passes through the liver. This applies to phytoestrogens and industrial estrogens as well as to the natural estrogens of the body. At a certain point, the increased estrogen and decreased thyroid and progesterone cause infertility, but

before that point is reached, the hyperestrogenism causes a great variety of birth defects. Deformities of the male genitals, and later, testicular cancer in the sons and breast cancer in the daughters, are produced by the combination of toxins and nutritional deficiencies.

Vitamin E

Estrogen Antagonist, Energy Promoter, and Anti-Inflammatory

Ray Peat's Newsletter, 2006

POLITICAL scientists have recognized the process in which big corporations "capture" the governmental agencies that were created to regulate them. The editorial boards of professional journals can be captured even more cheaply than the agencies of government, and their influence can be even more valuable to industry.

If science impinges upon the plans of an industry, it can be managed into compliance, when the industry controls the journals and the agencies that fund research.

In the 1940s, it had already become clear to the estrogen industry that vitamin E research was impinging on its vital interests.

The Manhattan Project, that created the atomic bomb, also created a generation of scientific and bureaucratic zealots who ignored public health and safety to advance their projects and their careers, and changed the way science was done. At exactly the same time, the pharmaceutical industry was using its financial and political power to change the way medicine was practiced and taught, and the consequences for world health rivaled those of the nuclear industry.

In 1933 the physician R.J. Shute was aware of the problems associated with toxemia of pregnancy or preeclampsia. Especially among poorly nourished women, many pregnancies were complicated by circulatory problems, including cyclic bleeding, thrombosis, stroke, and hypertension, and these difficult pregnancies often ended in miscarriage or premature delivery, resulting in many serious health problems among the babies that survived.

At that time, both estrogen and vitamin E were being widely studied, though the exact structure of the tocopherol molecule wasn't defined until 1936–37. Vitamin E had been found to improve fertility of both male and female animals, and to prevent intrauterine death of the embryo or fetus, so it was called the "antisterility vitamin." Using it to prevent women from having miscarriages must have occurred to many people.

Animal research in the 1930s was also showing that estrogen had many toxic effects, including causing infertility or intrauterine death, connective tissue abnormalities, and excessive blood clotting. Dr. Shute

and his sons, Wilfred and Evan, were among those who considered vitamin E to be an antiestrogen. They found that it was very effective in preventing the clotting diseases of pregnancy.

Other researchers, who knew that progesterone protected against the toxic effects of estrogen, described vitamin E as the "progesterone-sparing agent," since so many of its antiestrogenic effects resembled those of progesterone.

The Shute brothers began using vitamin E to treat circulatory diseases in general, rather than just in pregnant women—blood clots, phlebitis, hypertension, heart disease, and diabetes all responded well to treatment with large doses.

Vitamin E, as its name indicates, was the fifth type of "vitamin" factor to be identified, and it received its name in 1922, even though its chemical structure hadn't been identified. The public quickly understood and accepted that certain substances in food were essential for life and health, so by 1940 practically all physicians were recommending the use of nutritional supplements.

If vitamin E was essential for human health, and achieved at least some of its amazing effects by opposing estrogen, then the synthetic estrogen industry had a problem.

Edward L. Bernays had already been in business for decades, teaching corporations and governments how to "engineer consent." After his work for the government to engineer support for entering the first world war, Bernays' next big job was for the tobacco industry. To convince women to smoke cigarettes, to achieve equality with men, he organized an Easter parade, Torches of Freedom, in which thousands of women marched smoking their freedom torches. In association with the American Medical Association (the editor of *JAMA* actually helped the tobacco industry design its campaigns), Bernays ran a campaign to convince Americans that smoking was good for the health.

The drug industry began using his techniques in sometimes crude but always effective ways. Estrogen was named "the female hormone;" natural hormones, including estrogen and progesterone, were claimed, without any research, to be inactive when taken orally. Physician-shills were created to claim wonderful effects for estrogen. The vitamin status of the tocopherols was denied; as recently as the 1970s (and maybe later), university professors of dietetics were flatly saying "no one needs vitamin E."

Very little research showing the curative effects of vitamin E in human diseases was allowed to be published, so it was only occasionally necessary to openly denounce vitamin E as worthless or dangerous. In 1981, the journal of the AMA published an article reviewing the "toxic" effects of vitamin E. Since I had read all of the articles cited, I realized that the author was claiming that whenever vitamin E changed something, the change was harmful, even though the original publication had described the effect as beneficial.

Although *JAMA* was eventually forced to give up its revenue from cigarette advertising, it didn't suffer at all, because of the vast advertising campaigns of the estrogen industry. *JAMA* obviously wouldn't want to publish anything suggesting that vitamin E, or progesterone, or thyroid, might be beneficial because of its antagonism of the harmful effects of estrogen.

Estrogen causes changes in the uterus that prevent implantation of the embryo, and that impair support for its development if it has already implanted. It decreases the availability of oxygen to the embryo, while vitamin E increases it.

My dissertation adviser, A.L. Soderwall, did a series of experiments in which he showed that providing hamsters with extra vitamin E postponed the onset of infertility in middle age. In my experiments, vitamin E increased the amount of oxygen in the uterus, correcting an oxygen deficiency produced either by supplemental estrogen or by old age. Progesterone has similar effects on the delivery of oxygen to the uterus.

In the 1940s, the official definition of vitamin E's activity was changed. Instead of its effectiveness in preventing the death and resorption of embryos, or the degeneration of the testicles or brain or muscles, it was redefined as an antioxidant, preventing the oxidation of unsaturated oils.

Although some people continued to think of it as a protective factor against thrombosis, heart attacks, diabetes, and infertility, the medical establishment claimed that the prevention or cure of diseases in animals wasn't relevant to humans, and that a mere antioxidant couldn't prevent or cure any human disease.

The experiments that led to the identification of vitamin E involved feeding rats a diet containing rancid lard and, as a vitamin A supplement,

cod liver oil. Both of these contained large amounts of polyunsaturated oils.

From 1929 to the early 1930s, other researchers were claiming to have demonstrated that the polyunsaturated fatty acids were nutritionally essential. These experiments, like the vitamin E experiments, were done on rats, but the medical establishment was satisfied that rat experiments proved that humans need linoleic or linolenic acid, while they refused to accept that vitamin E was essential for humans. When, in the 1940s, a group of vitamin B_6 researchers showed that the supposed "essential fatty acid deficiency" could be cured by a supplement of vitamin B_6, it became apparent that the polyunsaturated fatty acids slowed metabolism, and reduced all nutritional needs. The thyroid hormone was powerfully suppressed by the "essential" fatty acids.

When we consider the two sets of experiments together, their outstanding feature is the toxicity of the polyunsaturated oils, which in one kind of experiment suppressed metabolism, and in the other kind of experiment created a variety of degenerative conditions.

By the late 1940s and early 1950s, estrogens of various sorts had been synthesized from hydrocarbons, and were being recommended to prevent miscarriages, because "estrogen is the female hormone." The meat industry had found that the polyunsaturated oils were valuable in animal feed, since they suppressed metabolism and made it cheaper to fatten the animals, and these antithyroid oils were next marketed as "heart protective" human foods, though by suppressing the thyroid and destroying vitamin E, they actually contributed to both heart disease and cancer. (Giving estrogen to livestock to improve their feed efficiency, and to people "to prevent heart attacks," was an interesting parallel to the oil promotional campaigns.)

The influence of the food oil industry kept researchers away from the idea that these oils were not safe for food use, and instead tended to support the idea that vitamin E is just an antioxidant, and that the seed oils were the best way to get vitamin E in the diet.

The antifertility effects of the polyunsaturated oils, demonstrated in the vitamin E experiments, weren't at the time understood to have anything to do with estrogen's antifertility effects. But to understand vitamin E, I think we have to consider the close interactions between estrogen and the polyunsatured fatty acids (PUFA). Their actions are closely intertwined, and are antagonized by a variety of energizing and

stabiliizing substances, including saturated fats, progesterone, thyroid, vitamin E, and aspirin.

Generally, chemicals that inhibit enzymes are toxic, producing some sort of symptom or deterioration. But a group of enzymes related to estrogen and PUFA are inhibited by these protective substances. Although under our present diet, these enzymes metabolize the PUFA, in the fetus and newborn they act on our endogenous fats, the series related to the Mead acids. The Mead acid is antiinflammatory, and broadly protective. The dietary PUFA interfere with these natural protective substances,

The enzymes that, if we didn't eat PUFA, would be regulating the Mead series, being activated in response to stress, would be producing antistress substances, which would limit the stress reaction. But as we become increasingly saturated with the anti-vitamin E fats, these enzymes, instead of stopping inflammation, promote it and cause tissue injury. The remaining stress limiting factors, such as progesterone, by correcting the distortions caused by stress, tend to eliminate the conditions which activated the enzymes—in a very indirect form of inhibition.

Many of the events involved in inflammation are increased by estrogen, and decreased by vitamin E. Estrogen causes capillaries to become leaky; vitamin E does the opposite. Estrogen increases platelet aggregation, and decreases a factor that inhibits platelet aggregation; vitamin E does the opposite.

Excess clotting is known to be caused by too much estrogen, and also by a vitamin E deficiency.

Clotting leads to fibrosis, and there is clear evidence that vitamin E prevents and cures fibrotic diseases, but this still isn't generally accepted by the powerful medical institutions. Estrogen and polyunsaturated fats increase fibrosis.

Estrogen increases progstaglandin synthesis, vitamin E decreases their synthesis; estrogen increases the activity of the enzymes COX and LOX, vitamin E decreases their activitiy.[1–3] Estrogen releases enzymes from lysosomes, vitamin E inhibits their release. Beta-glucuronidase, one of these enzymes, can release estrogen at the site of an inflammation.

Estrogen often increases intracellular calcium and protein kinase C, vitamin E has generally opposite effects.

The polyunsaturated fatty acids and their derivatives, the prostaglandins, act as effectors, or amplifiers, of estrogen's actions.

If vitamin E is acting as a protectant against the polyunsaturated fatty acids, that in itself would account for at least some of its antiestrogenic effects.

Besides antagonizing some of the end effects of the toxic fatty acids, vitamin E inhibits lipolysis, lowering the concentration of free fatty acids (the opposite of estrogen's effect), and it also binds to, and inactivates, free fatty acids. The long saturated carbon chain is very important for its full functioning, and this saturated chain might allow it to serve as a substitute for the omega -9 fats, from which the Mead acid is formed. The unsaturated tocotrienols have hardly been tested for the spectrum of true vitamin E activity, and animal studies have suggested that it may be toxic, since it caused liver enlargement.

One possibly crucial protective effect of vitamin E against the polyunsaturated fatty acids that hasn't been explored is the direct destruction of linolenic and linoleic acid. It is known that bacterial vitamin E is involved in the saturation of unsaturated fatty acids, and it is also known that intestinal bacteria turn linoleic and linolenic acids into the fully saturated stearic acid.

> *"No metabolic function is known for alpha-tocopherolquinol or its quinone other than as a cofactor in the biohydrogenation of unsaturated fatty acids that can be carried out by only a few organisms."*[4]

> *"Linoleic acid was significantly decreased ($P < 0.001$) and there was a significant rise ($P < 0.05$) in its hydrogenation product, stearic acid. Linolenic acid was also significantly decreased..." "The study provides evidence that bacteria from the human colon can hydrogenate C_{18} essential polyunsaturated fatty acids."*[5]

Because of the way in which the decision to call vitamin E a simple antioxidant was conditioned by the historical setting, there has been a reluctance, until recently, to give much weight to the pathogenicity of lipid peroxidation and free radicals, partly because lipid peroxidation is only a minor part of the toxicity of the polyunsaturated oils, and there was little support for the investigation of the real nature of their toxicity. This environment has even distorted the actual antioxidant value of the various forms of vitamin E.[6]

The people who say that vitamin E is nothing but an antioxidant sometimes take other antioxidants, with, or instead of, vitamin E. BHT, BHA, and many natural compounds (derived from industrial and agricultural wastes) are often said to be "better than vitamin E" as antioxidants. Anything that can be oxidized and reduced (melatonin, estrogen, tryptophan, carotene, etc.) will function as an antioxidant in some system, but in other circumstances, it can be a pro-oxidant.

The people who think there is benefit in the abstract "antioxidant" function seem to be thinking in terms of something that will, like a ubiquitous fire department, put out every little fire as soon as it starts. I think it's more appropriate to think of the biological antioxidant systems as programs for controlling the arsonists before they can set the fires.

Since the requirement for vitamin E decreases as the consumption of unsaturated fats decreases, the requirement, if any, would be very small if we didn't eat significant quantities of those fats.

In the years since the tocopherols were identified as vitamin E, the material sold for research and for use as a nutritional supplement has changed drastically several times, even when it has been given a specific chemical identity, such as mixed tocopherols or d-alpha tocopherol. Variations in viscosity and color, caused by changes in the impurities, have undoubtedly influenced its biological effects, but the ideology about its antioxidant value has kept researchers from finding out what a particular batch of it really is and what it really does.

> *"We compared the effect of a mixed tocopherol preparation with that of alpha-tocopherol alone on superoxide dismutase (SOD) activity and iNOS expression in cultured myocytes exposed to H-R." "Both tocopherol preparations attenuated cell injury..." "However, mixed-tocopherol preparation was much superior to alpha-tocopherol in terms of myocyte protection..." "Lack of efficacy of commercial tocopherol preparations in clinical trials may reflect absence of gamma- and delta-tocopherols."*[7]

Keeping our diet as free as possible of the polyunsaturated fats, to create something like the "deficiency" state that is so protective (against cancer, trauma, poison, shock, inflammation, infection, etc.) in the animal experiments, seems preferable to trying to saturate ourselves with

antioxidants, considering the imperfectly defined nature of the vitamin E products, and the known toxicity of many of the other antioxidants on the market.

The carcinogenic properties of the polyunsaturated fats have been known for more than 50 years, as has the principle of extending the life span by restricted feeding. More recently several studies have demonstrated that the long lived species contain fewer highly unsaturated fats than the short lived species. Restriction of calories prevents the lipids in the brain, heart, and liver from becoming more unsaturated with aging.[8–11]

When cells are grown in tissue culture without the "essential fatty acids," they become "deficient," and in that state are very resistant to chemical injury, and can be grown indefinitely. Besides being a simple demonstration of the way in which the polyunsaturated fats sensitize cells to injury,[12] these experiments must be an embarrassment to the people who base their argument for the oils' essentiality on a supposed requirement for "making cell membranes." Since the cells can multiply nicely in their deficient state, we have to conclude that the oils aren't needed for "membranes," or maybe that cells resist injury better "without membranes."

In the opposite direction, an excess of insulin or prolactin, or a deficiency of vitamin E, increases the activity of the enzymes that convert linoleic acid into the more highly unsaturated fatty acids. Excess insulin and prolactin are crucially involved in many degenerative diseases.

The highly unsaturated fats suppress respiration in many ways, and these trends toward increased unsaturation with aging, endocrine stress, and vitamin E deficiency parallel the life-long trend toward lower energy production from respiration. Many studies show that vitamin E can protect and improve mitochondrial energy production.[13–17] But the state of so-called essential fatty acid deficiency not only makes mitochondria very resistant to injury, it greatly intensifies their energy production. Vitamin E supplementation is seldom as effective as the absence of the toxic oils.

Many nutrition charts no longer list liver as a good source of vitamin E, but a large portion of an animal's vitamin E is in its liver. This bias in the dietetic literature can be traced to various sources, but a major influence was the campaign in the 1970s by the drug companies that had patented new forms of synthetic "vitamin A." They had physicians and

professors fabricate stories about the great toxicity of natural vitamin A, and placed the stories in national magazines, to clear the field for their supposedly non-toxic products, which have turned out to be disastrously toxic. The result is that many people have fearfully stopped eating liver, because of its vitamin A. The other vitamins in liver, including vitamin K, function very closely with vitamin E, and the stably stored forms of vitamin E are likely to be a good approximation for our needs.

There is still a strong division between what people can say in their professional publications, and what they believe. A man who was influential in designating vitamin E as an antioxidant, M.K. Horwitt, complained when the government raised its recommended vitamin E intake by 50 %, because it wasn't supported by new data, and because millions of people get only 10 mg per day and "are healthy." But he has been taking 200 mg daily (plus aspirin) for many years. He apparently doesn't have very much confidence in the ideas he advocates publicly.

Water

Swelling, Tension, Pain, Fatigue, Aging

Ray Peat's Newsletter, 2009

I have spoken to many people who believe they should drink "8 glasses of water every day," in addition to their normal foods, even if they don't feel thirsty. Many doctors still recite this dangerous slogan, but the addition of the qualifying phrase, "or other liquids," has become common.

The amount of water a person needs is extremely variable, depending on things such as metabolic rate, activity, and the temperature and humidity of the air. Working hard in hot, dry weather, it's possible to drink more than two quarts per hour for more than eight hours, without forming any urine, because all of the water is lost by evaporation. But in very hot, humid weather, a person with a low metabolic rate can be endangered by the smallest amount of water.[1]

Most foods contain a considerable amount of water, usually more than 70% of their weight, and some water is produced in cells by metabolism. The function of water in the organism has been mystified and neglected because of some deeply rooted cultural images of the nature of organisms and their cellular make-up.

One silly image that has been perpetuated by schools and textbooks is that biochemistry consists of chemical reactions that occur in substances dissolved in water, and that the water is retained by cells because they are enclosed by an oily membrane, and because of the osmotic forces produced by the dissolved substances. Most grade school kids have seen an osmometer made from an egg, in which the egg causes a column of water to rise, and have heard the explanation that this has something to do with the way cells work. Membrane pumps are invoked to explain the differences in solute concentrations and "osmotic pressure" inside and outside cells. The story is that invisible things on the surface of a cell (in its "membrane") force dissolved molecules to move in ways that they wouldn't move spontaneously by diffusion, and that water passively follows the "actively transported" solutes. But the evidence shows that both water and its solutes are regulated by the bulk phase of the cell, not its surface.

In some cultural settings, animism has a kind of charm (water sprites, and such), but in the culture of medicine and biology, the animistic conceptualization of cells and their mechanisms has been very destructive, because it gets in the way of coherent understanding of physiology. Practically every disease would be approached differently if the physiology of water and ions were allowed to advance beyond the animistic doctrines of mainstream medicine, such as the "membrane pumps." If all the substances that are said to be "actively transported" by pumps into, or out of, cells are considered, the amount of energy required to operate the pumps is at least 15 times larger than the total energy available to cells. "Specific" pumps are commonly invoked even for novel synthetic chemicals, to explain their unequal distribution, inside and outside cells. In many biological situations water is ignored, but when it becomes an issue, its distribution is usually mechanistically subordinated to the solutes that are actively "pumped."

Cells aren't osmometers, in the sense the textbooks say. They do control their water content, but no "membrane pumps" are needed. It's more accurate to think of the water of cells as being "dissolved in cells," somewhat the way water is contained in jello or boiled eggs. The cell controls its hydration by the processes that control its structure, its metabolism, and movements, because water is part of its deepest structures and essential functions. The cell's adjustments to changes of hydration and volume appear to be regulated by contractile proteins and energy metabolism.[2]

Any stress or energy deficit that disturbs cellular structure or function disturbs the interactions among water, proteins, and other components of the cell. Excitation causes a cell to take up extra water, not by osmosis resulting from an increase in the concentration of solutes in the cell, or because the membrane has become porous, but because the structural proteins of the cell have momentarily increased their affinity for water.

This increased affinity is similar to the process that causes a gel to swell in the presence of alkalinity, and it is related to the process called electroosmosis, in which water moves toward a higher negative charge. Intense excitation or stress increases the cell's electrically negative charges, and causes it to become more alkaline and to swell. Swelling and alkalinity cause the cell to begin the synthesis of DNA, in preparation for cell division. Mitogens and carcinogens, including estrogen, cause cells to become alkaline and to swell, and substances that block the

cell's alkalinization (such as the diuretics acetazolamide and amiloride) inhibit cell division. Prolonged alkaline stress alone can cause malignant transformation of kidney cells.[3]

The general idea of "stress" is useful, because it includes processes such as fatigue, osmotic pressure changes, disturbed pH, and the enzyme changes that follow, producing substances such as lactic acid, nitric oxide, polyamines, estrogen, serotonin, and many more specific mediators. But paying attention to the physical factors involved in a stress reaction is important, if we are to see the organism integrally, rather than as a collection of "specific biological mechanisms," involving things like the pixie-powered "membrane pumps."

When a cell shrinks under hyperosmolar conditions, its metabolism becomes catabolic, breaking down proteins and glycogen, and sometimes producing lactic acid, which results in an alkaline shift, increasing the cell's affinity for water, and causing it to return to normal size. A slight degree of hyperosmolarity increases the cell's metabolic rate.

Swelling in hypo-osmolar conditions, i.e, with an excess of water, is anabolic, leading to cellular proliferation, and inhibiting the breakdown of protein and glycogen.

Respiring cells are always producing some water, by transferring hydrogen from fuel molecules to oxygen. Respiration also produces carbon dioxide, which in itself is a Lewis acid (meaning that it binds electrons, rather than releasing protons), that associates with cellular proteins, acidifying them in the process. A large amount of carbon dioxide can exist inside cells in the bound form. Acidified cytoplasm (like any other mostly acidic polymer-gel) releases water and sodium. (This process is physically analogous to the process of flushing a water softener with salt, or a demineralizer with acid, to reactivate it.)

Besides binding with the cytoplasm, the carbon dioxide can be changed into carbonic acid, by chemically combining with water. Carbonic acid is hydrophilic, and so it quickly leaves the cell, taking with it some of the oppositely charged ions, such as calcium and sodium. The formation of carbonic acid, which is constantly streaming out of the respiring cell, causes some water and some positively ionized metals to leave the cell, in an "active" process, that doesn't require any mysterious pumps.

As the blood passes through the lungs, carbon dioxide leaves the system, and as carbonic acid is converted to carbon dioxide, water is left

behind in the blood, along with the counterions (of alkaline metals or earths), accounting for slight differences in pH and osmolarity between the bloodstream and the tissue cells. Some experiments suggest that the normal osmolarity of various tissues is 2 or 3 times higher than that of the blood, which is called "isosmolar" or isotonic.

The kidneys adjust the osmolarity of the blood by allowing water and solutes to leave the bloodstream, in proportions that usually keep the body fluids in balance with cells. The kidneys are able to compensate for many of the imbalances produced by stress and inappropriate diets, for example by forming ammonia and carbon dioxide, to compensate for imbalances in the alkalis and acids that are being delivered to the blood by other organs. Because of the kidneys' great ability to regulate the flow of solutes between the blood and the forming urine, the "membrane pumps" have great importance for medical nephrologists. But the more extreme the "active transport" is, the more obvious it becomes that processes other than "membrane pumps" are responsible.

Some lizards and sea birds have glands near their noses that are called salt glands, because of their ability to secrete salt. The salt gland is probably the most extreme case of active transport, but its physiology is very similar to the physiology of any other secretory gland or membrane, such as tear glands and sweat glands. The mechanism of salt excretion in these glands should really settle the issue of how active transport works, but most nephrologists, oculists, and medical researchers in general aren't interested in salt glands.

Carbon dioxide is the driving force in the salt gland. The constant formation of CO_2, and its loss into the air, allows a high concentration of salt to be excreted. Blocking the interchange of CO_2 and carbonic acid, with acetazolamide, or inhibiting the formation of CO_2, prevents the excretion of salt.

Since respiratory metabolism, governed by the thyroid hormone, is our main source of carbon dioxide, it's obvious that thyroid deficiency should impair our ability to regulate water and solutes, such as salt. An organism that illustrates this function of thyroid is the young salmon, when it leaves a freshwater river to begin its life in the ocean. As it converts its physiology to tolerate the salty environment, its thyroid hormone surges. When it's mature, and returns to the fresh water to spawn, its prolactin rises sharply. In experiments with rodents, it

has been found that drinking a large amount of water increases their prolactin, but the same amount of water, with added salt, doesn't.

Hypothyroidism is typically associated with increased prolactin secretion. Hypothyroid people typically retain water, while losing salt, so the hypothyroid state is analogous to the salmon that has returned to the river, and to the mice that drink too much salt-free water.

The typical hypothyroid person loses salt rapidly in the urine (and probably in the sweat, too, though that is usually diagnosed as cystic fibrosis), and retains water, diluting the urine less than normal. The reduced production of carbon dioxide, with increased susceptibility to producing lactate and ammonium, causes the cells to be more alkaline than normal, increasing their affinity for water. The rise of estrogen that usually accompanies hypothyroidism also increases intracellular pH, loss of sodium, and over-hydration of the blood.

Hypothyroid muscles typically retain excess water, and fatigue easily, taking up more water than normal during exertion. In childhood, mild hypothyroidism often causes the leg muscles to swell and ache in the evenings, with what have been called "growing pains." When the problem is more extreme, all the skeletal muscles can become very large (Hoffman syndrome), because of the anabolic effect of over-hydration. Enlargement of any muscle can result from the excessive hydration produced by thyroid deficiency, but when it happens to the muscles behind the eyes,[4] it often leads to a diagnosis of hyperthyroidism, rather than hypothyroidism.

The little kids with the Hoffman syndrome don't have the bloated myxedematous appearance that's often associated with hypothyroidism. They look athletic to a ridiculous degree, like miniature body-builders. But after a few weeks of treatment with thyroid, they regain the slender appearance that's normal for their age. The swollen state actually supports enlargement of the muscle, and the cellular processes are probably closely related to the muscle swelling and growth produced by exercise. The growth of the muscle cell during swelling seems to be the result of normal repair processes, in a context of reduced turnover of cellular proteins.

The people who believe in membrane pumps that maintain normal solute distributions by active transport know that the pumps would require energy (far more than the cell can produce, but they don't confront that issue), and so their view requires that they assign a great part of the

cell's resources just to maintaining ionic homeostasis, and the result of that is that they tend to neglect the actual energy economy of the cell, which is primarily devoted to the adaptive renewal of the cell structure and enzyme systems, not to driving the systems that don't exist.

The "anabolic" balance of the swollen cell is the result of decreased turnover of the cell's components. The higher rate of metabolism produced by adequate thyroid function maintains a high rate of renewal of the cell's systems, keeping the cell constantly adjusted to slight changes in the organism's needs. The evidence of a high rate of bone turnover is sometimes taken as evidence that thyroid can cause osteoporosis.

Later, in a more mature person, chronically fatigued and painful muscles that at one time would have been diagnosed as rheumatism, may be diagnosed as fibromyalgia. Most doctors are reluctant to prescribe thyroid supplements for the problem, but the association of elevated prolactin with the muscle disorder is now generally recognized.

The hypo-osmolar blood of hypothyroidism, increasing the excitability of vascular endothelium and smooth muscle, is probably a mechanism contributing to the high blood pressure of hypothyroidism. The swelling produced in vascular endothelium by hypo-osmotic plasma causes these cells to take up fats, contributing to the development of atherosclerosis. The generalized leakiness affects all cells (see *Leakiness* newsletter), and can contribute to reduced blood volume, and problems such as orthostatic hypotension. The swollen endothelium is stickier, and this is suspected to support the metastasis of cancer cells. Inflammation-related proteins, including CRP, are increased by the hypothyroid hyperhydration. The heart muscle itself can swell, leading to congestive heart failure.

Some of the nerve problems associated with hypothyroidism (e.g., carpal tunnel syndrome and "foot drop") are blamed on compression of the nerves, from swelling of surrounding tissues, but the evidence is clear that hypothyroidism causes swelling in the nerve cells themselves. For example, in hypothyroidism, nerves are slow to respond to stimulation, and their conduction of the impulse is slow. These changes are the same as those produced by hyper-hydration caused by other means. Hypothyroid nerves are easily fatigued, and fatigued nerves take up a large amount of water. Swelling of the spinal cord is probably responsible for the "spinal stenosis" commonly seen in domestic animals and people;

the mobility of intracellular water molecules is distinctly increased in patients with compression of the spinal cord.[5,6]

The hyperhydration of hypothyroidism has been known to cause swelling and softening of cartilage, with deformation of joints, but somehow it has never dawned on surgeons that this process would lead to deformation of intervertebral disks.

It has been known for a long time that hyperhydration can produce seizures; at one time, neurologists would test for epilepsy by having the patient drink a pint of water. Although there are many reasons to think that the hyperhydration produced by hypothyroidism is a factor in epilepsy, physicians have been very reluctant to consider the possibility, because they generally think of thyroid hormone as a stimulant, and believe that "stimulants" are necessarily inappropriate for people with epilepsy.

While it's true that the thyroid hormone increases sensitivity to adrenaline, its most noticeable effect is in improving the ability to relax, including the ability to sleep soundly and restfully. And it happens that increasing norepinephrine (the brain's locally produced form of adrenaline) helps to prevent seizures.[7]

Cell swelling increases the sensitivity of nerves, and hyperosmotic shrinkage lowers their sensitivity. Increasing carbon dioxide helps to reduce the hydration of tissue (for example, the hydration and thickness of the cornea are decreased when carbon dioxide is increased), and increasing carbon dioxide is known to inhibit epileptic seizures. Another diagnostic trick of neurologists was to have the patient hyperventilate; it would often bring on a seizure. The diuretic acetazolamide, which increases the body's carbon dioxide and reduces water retention, is very effective for preventing seizures.

The sleep-inducing effect of salty food is probably related to the anti-excitatory effects of hyperosmolarity, of adequate thyroid function, and of carbon dioxide.

Degenerative diseases, especially cancer, heart disease, and brain diseases, are less prevalent in populations that live at a high altitude. When oxygen pressure is low, the lungs lose carbon dioxide more slowly, and so the amount of carbon dioxide retained in the body is greater. If the basic problem in hypothyroidism is the deficient production of carbon dioxide causing excessive loss of salt and retention of water, resulting in hypo-osmotic body fluids, then we would expect people at high altitude

to have better retention of salt, more loss of water, and more hypertonic body fluids. That has been observed in many studies. The increased rate of metabolism at altitude would be consistent with the relatively active "catabolism" of the slightly hyperosmotic condition.

After the drug companies began, in the late 1950s, marketing some newly discovered (thiazide) diuretics, which cause sodium to be lost in the urine, their advertising campaigns created a cultish belief that salt caused hypertension. They convinced a whole generation of physicians that pregnant women should limit salt in their diet, take a diuretic preventively, and restrict calories to prevent "excessive" weight gain. Millions of women and their babies were harmed by that cult.

Pre-eclampsia and pregnancy toxemia have been corrected[8] by both increased dietary protein and increased salt, which improve circulation, lower blood pressure, and prevent seizures, while reducing vascular leakiness. The effectiveness of increased salt in pre-eclampsia led me to suggest it for women with premenstrual edema, because both conditions typically involve high estrogen, hyponatremia, and a tendency toward hypo-osmolarity. Estrogen itself causes sodium loss, reduced osmolarity, and increased capillary leakiness. Combined with a high protein diet, eating a little extra salt usually helps to correct a variety of problems involving edema, poor circulation, and high blood pressure.

The danger of salt restriction in pregnancy has hardly been recognized by most physicians, and its danger in analogous physiological situations is much farther from their consideration.

One of the things that happen when there isn't enough sodium in the diet is that more aldosterone is synthesized. Aldosterone causes less sodium to be lost in the urine and sweat, but it achieves that at the expense of the increased loss of potassium, magnesium, and probably calcium. The loss of potassium leads to vasoconstriction, which contributes to heart and kidney failure and high blood pressure. The loss of magnesium contributes to vasoconstriction, inflammation, and bone loss. Magnesium deficiency is extremely common, but a little extra salt in the diet makes it easier to retain the magnesium in our foods.

Darkness and hypothyroidism both reduce the activity of cytochrome oxidase, making cells more susceptible to stress. A promoter of excitotoxicity, ouabain, or a lack of salt, can function as the equivalent of darkness, in resetting the biological rhythms.[9,10]

Bone loss occurs almost entirely during the night, and the nocturnal rise in cortisol and prolactin has strongly catabolic effects, but many other pro-inflammatory substances also rise during the night, and are probably the basic cause of the increased catabolism. Increased salt in the diet appears to improve some aspects of calcium metabolism, such as reducing parathyroid hormone and increasing ionized calcium, when the diet is deficient in calcium.[11]

The kidneys can produce large amounts of carbon dioxide and ammonia, in the process of preventing the loss of electrolytes, while allowing acid to be lost in the urine. The ammonia is produced by the breakdown of protein. During stress or fasting, the loss of tissue protein can be minimized by supplementing the minerals, potassium, sodium, magnesium, and calcium. Salt restriction can cause aldosterone to increase, and excess aldosterone causes potassium loss, and increases the use of protein to form ammonia.[12–14]

Aldosterone secretion increases during the night, and its rise is greater in depressed and stressed people. It inhibits energy metabolism, increases insulin resistance, and increases the formation of proinflammatory substances in fat cells.[15] During aging, salt restriction can produce an exaggerated nocturnal rise in aldosterone.

During the night, there are many changes that suggest that the thyroid functions are being blocked, for example a surge in the thyroid stimulating hormone, with T_4 and T_3 being lowest between 11 PM and 3 AM,[16] while temperature and energy production are at their lowest. This suggests that the problems of hypothyroidism will be most noticeable during the night.

Rheumatoid arthritis and asthma are two inflammatory conditions that are notoriously worse during the night. Melatonin has been reported to be higher in patients with severe asthma and rheumatoid arthritis, and to promote the secretion of a variety of other pro-inflammatory substances. The peak of melatonin secretion is followed by the peak of aldosterone, and a little later by the peak of cortisol.

The use of bright light (which suppresses melatonin) to treat depression probably helps to inhibit the production of aldosterone, which is strongly associated with depression.

Both aldosterone and melatonin can contribute to the contraction of smooth muscle in blood vessels. Constriction of blood vessels in the kidneys helps to conserve water, which is adaptive if blood volume has

been reduced because of a sodium deficiency. When blood vessels are inappropriately constricted, the blood pressure rises, while organs don't receive as much blood circulation as they need. This impaired circulation seems to be what causes the kidney damage associated with high blood pressure, which can eventually lead to heart failure and multiple organ failure.

Progesterone, which helps to maintain blood volume (partly by preventing vascular leakiness, preventing excessive sodium loss and by supporting albumin synthesis) antagonizes aldosterone. Aldosterone antagonists are now being recognized as effective treatments for hypertension, water retention, congestive heart failure, arrhythmia, diabetes, kidney disease, and a great variety of inflammatory problems. (Synthetic drugs to antagonize aldosterone are most effective when they are most like natural progesterone.) Since aldosterone contributes to fibrosis of the heart and kidneys (nephrosclerosis), progesterone, the "antifibromatogenic steroid," should be helpful for those problems that have been considered irreversible. Aldosterone appears to contribute to the hyperglycemia of diabetes itself, and not just to its complications, by interfering with the interactions of insulin and cortisol.[17]

One of progesterone's fundamental actions is to cause estrogen "receptors" to disintegrate; hypertonicity has this effect in some situations. Estrogen's effects are largely produced by increased tissue hydration.

Aldosterone causes cells to take up sodium, while increasing their pH, i.e., raising their alkalinity.[18] Intracellular sodium has long been known to be a factor, along with swelling and alkalinity, in stimulating cell division.[19] A lack of salt stimulates the formation of serotonin, which in turn stimulates aldosterone synthesis—that is, a sodium restricted diet activates processes that cause cells to take up sodium inappropriately, in a situation reminiscent of the calcium deficient diet causing inappropriate calcification.

Aldosterone, like stress or hypo-osmolarity, activates the enzyme (ODC) which produces the polyamines, that promote cell division, and that can probably account for some of the harmful effects of excessive aldosterone.

Eating salty food around bedtime usually has a sleep-inducing effect, and it helps to maintain blood volume (which tends to decrease during the night), and to restrain the nocturnal rise of aldosterone, and other indicators of stress or inflammation. Eating gelatin, which lacks trypto-

phan, will reduce the formation of serotonin, and is likely to limit the formation of aldosterone.

Pregnenolone can sometimes very quickly allow swollen tissues to release their water. This function is probably closely related to its antifibromatogenic function, since swelling and leaking set the stage for fibrosis.

Hyperosmotic sodium chloride solutions (e.g., 7.5 %) are being used more often for treating trauma and shock, because the concentrated solution increases blood volume by removing water from the extravascular spaces, unlike the "isotonic" saline (0.9 % sodium chloride), which usually adds to the edema by leaking out of the blood vessels.

A 5 % sodium chloride solution is effective for promoting healing of damaged corneas, and solutions of 5 % to 10 % sodium chloride are effective for accelerating the healing of wounds and ulcers. Other hypertonic solutions, for example glucose or urea, have been used therapeutically, but sodium chloride seems to be the most effective in a variety of situations.

Thyroid hormone, by maintaining oxidative metabolism with the production of carbon dioxide, is highly protective against excessive water retention and loss of sodium and magnesium.

Sometimes doctors recommend that constipated people should drink extra water, "to soften the stool." The colon is where water is removed from the intestinal contents, and when it is inflamed, it removes too much water. Several decades ago, it was recognized[20] that hypertonic saline, given intravenously, would stimulate intestinal peristalsis, and could be used to treat paralytic ileus and intestinal obstruction.

When water is taken orally, it is absorbed high in the intestine, long before it reaches the colon, so the recommendation to drink water for constipation can produce a situation that's the opposite of intravenous hypertonic saline, by diluting the blood. Using a hypertonic salt solution as an enema can have the same beneficial effect on the intestine as the intravenous treatment.

Constipation physiology is probably analogous to the physiology of congestive heart failure, in which muscles are weakened and fatigued by swelling.

In recent decades, the prevalence of congestive heart failure has increased tremendously, so that it is now often called an epidemic. Hyponatremia (too little salt, or too much water) is a recognized "risk

factor" for congestive heart failure. In the failing heart, the muscle cells are swollen, causing the heart wall to stiffen, weakening its ability to pump. Osmotically shrinking the cells can restore their function.

The swollen heart, like any muscle, loses the ability to quickly and completely relax, and so it doesn't fill adequately between contractions. Elastic tissues, such as arteries and lungs, stiffen when they are overhydrated, losing their normal functions. In small blood vessels, swelling narrows the channel, increasing resistance to the flow of blood.

When people force themselves to drink a certain amount of water every day, even when they don't feel thirsty, they are activating complex adaptive processes unnecessarily. Thirst is the best guide to the amount of fluid needed.

When extra water consumption is combined with a low salt diet—as physicians have so often recommended—a healthy person can adapt easily, but for a hypothyroid person it can have disastrous effects.

When Energy Fails

Edema, Heart Failure, Hypertension, Sarcopenia, etc.

Ray Peat's Newsletter, 2013

More than 100 years ago the idea of a morphogenetic field was proposed by A.G. Gurwitsch, as a way to explain the orderly movements of cells in embryos and growing tissues, and to understand the principles that cause cells to change appropriately when their location in the organism changes. For 30 years, the concept guided research in embryology, but also led to important discoveries in the biology of cancer, aging, wound repair, and other important areas. But by the late 1940s, a more abstract approach to biology, based on the gene doctrine of Mendel and Weismann, took charge of academic and governmental biological research. This ideology at first said that organisms are determined by unchanging units of inheritance, "genes," and later when genes were found to be susceptible to mutation, the changes were said to be always random. The Central Dogma of the ideology was that any meaningful, adaptive changes that occur in an organism can't influence the genes. For many years, adaptive changes were said to be nothing but changes in the size or function of existing cells, because the cells of the major organs of the body were supposed to be created before birth, or in infancy.

Besides the purely ideological commitment to the theory of genes, there were other influences that contributed to the culture of Molecular Biology. People learned histology from slides or pictures made by killing, hardening, dehydrating, and slicing parts of organisms. Biochemists studied the chemistry of life mainly by grinding cells or tissues, and extracting water-soluble materials to study the actions of enzymes on various materials. These unrealistic artifacts filled the textbooks and the minds of generations of biologists and physicians. The culture of molecular biology used these artifacts to create theories of embryology and physiology, and holistic ideas such as the developmental field were disregarded.

The mental image of a living organism that has been created by that culture is simply wrong. The concept of a developmental field is essential for understanding embryology, because things that exist on a scale bigger than molecules and cells govern the functions of the molecules and cells, and the principles of embryology don't arbitrarily stop operating at birth,

but can be seen to continue operating during maturity and aging. The interactions of cells with their environment are different at different stages of life, but there are commonalities that are extremely important.

The processes that govern the pregnant woman's blood circulation, in sustaining the development of a fetus, are very similar to the processes that govern anyone's blood circulation, providing for the maintenance and renewal of all the body's organs. The common problems of pregnancy involving the circulatory system can provide insights into the problems of the various organs that have been the focus of the medical specialties, and to some basic medical issues, including aging, obesity, and inflammation.

The development of a fertilized egg into an embryo consumes energy at a very high rate, and the way the embryo develops depends on a continuously adequate supply of oxygen and sugar, and other nutrients. The intense flow of energy through each stage of a developing structure shapes the following stage. The necessary energy and materials are provided abundantly by the mother's blood. When the development has advanced far enough to make life possible outside the uterus, energy will be used more slowly, for growth, maintenance, and renewal of tissues.

Failure to renew cells and tissues leads to the loss of function and substance. Bones and muscles get weaker and smaller with aging. Diminished bone substance, osteopenia, is paralleled, at roughly the same rate, by the progressive loss of muscle mass, sarcopenia (or myopenia). The structure of aging tissue changes, with collagen tending to fill the spaces left by the disappearing cells. It's also common for fat cells to increase, as muscle cells disappear.

When conditions are ideal, as during healthy development in the uterus, tissue damage is corrected by the multiplication of cells to replace any that were lost. But when conditions are less perfect, injuries are imperfectly repaired, usually with highly collagenous scar tissue bridging the area that was destroyed. During this imperfect repair, there is inflammation, which apparently exists to the extent that the substances needed for regeneration are lacking. For example, when oxygen is lacking, lactic acid is likely to be produced, along with increases of pro-inflammatory regulators such as histamine and serotonin, leading to the loss of many important proteins and functions, and the over-production of collagen instead.

Since cellular renewal of tissues, in a healthy individual, is a constant process, we can think of the metabolic rate of a healthy adult as just what is needed to sustain this constant, limited sort of regeneration, but not quite intense enough to produce scarless healing of a wound (without special intervention).

If something reduces the systemic ability to produce energy, there will be a gap between the available energy and the energy needed for the constant turnover of cells in each tissue and organ, and a generalized inflammation will develop. The replacement of cells will be slowed, and the organism will mobilize the processes used for producing scar tissue, producing an excess of collagen, filling the spaces left by the lost cells.

We are susceptible to many things that interfere with energy production—the substitution of iron for copper in the respiratory enzyme, the absorption of endotoxin, the accumulation of PUFA, a deficiency of thyroid hormone, the formation of increased amounts of nitric oxide, serotonin, and histamine, etc. Different environments will condition the way the defensive mechanisms of inflammation are produced.

Toxemia of pregnancy, or preeclampsia, is a state of generalized inflammation, and some of the causes and remedies are known. Despite the predominance of crazy genetic theories of preeclampsia in 20th century medical literature, there was clear evidence (reviewed by Tom Brewer, Douglas Shanklin, and Jay Hodin) that it was caused by malnutrition, and that it could be cured by adequate protein, salt, and calcium.

The old medical practice of restricting salt intake during pregnancy was an important factor in causing it, so it's interesting to look at the effects of salt restriction as a treatment for hypertension.

The pregnant woman's blood volume expands, to permit the supply of energy to match the needs of the embryo. If the blood volume doesn't increase, or if it decreases, as in pregnancy toxemia, her blood pressure will increase. Typically, the decrease of blood volume is accompanied by an increase in the extracellular fluid, edema, resulting from leakage of fluid through the walls of the capillaries, and albumin appears in the urine as it leaks through the capillaries in the kidneys. The amount of blood pumped by the heart, however, is increased in toxemia,[1] showing that the increased blood pressure is at least partially compensating for the smaller volume of blood.

A similar situation, reduced blood volume and edema, can be seen[2] in "essential hypertension," the "unexplained" high blood pressure that occurs more often with increasing age and obesity. At the beginning of "essential hypertension," the amount of blood pumped is usually greater than normal.

In both situations, preeclampsia and essential hypertension, there is an increased amount of aldosterone, an adrenal steroid which allows the kidneys to retain sodium, and to lose potassium and ammonium instead. A restriction of salt in the diet causes more aldosterone to be produced, and increased salt in the diet causes aldosterone to decrease. One effect of aldosterone is to increase the production of a substance called vascular endothelial growth factor, VEGF, or vascular permeability factor, which causes capillaries to become leaky, and causes new blood vessels to grow.

While increased salt in the diet tends to lower both aldosterone and VEGF, reducing the leakiness of blood vessels, sodium also has a direct effect that tends to prevent the leakage of water and albumin out of the blood vessels, helping to maintain the blood volume which is needed to perfuse the kidneys, preventing them from producing signals to increase blood pressure and aldosterone. There is a large amount of albumin in the blood serum, and sodium ions associate with the negative electrical charges on the albumin molecule. This association causes the complex of albumin and sodium to attract a large amount of water, that is to exert osmotic or oncotic pressure. This oncotic pressure causes any excess extracellular water to be attracted into the blood vessels, preventing edema while maintaining the blood volume. When there is too little sodium, the albumin molecule itself easily leaves the blood stream along with the water.

Instead of considering the significance of sodium's effects on albumin, aldosterone, and VEGF, textbooks have often talked about the factors that "pump" sodium, and factors that specifically regulate the movement of water. Experiments in which an excess of aldosterone is combined with a high salt intake produce increased blood pressure, and—by invoking various genes—salt is said to cause hypertension in certain people. This reasoning is hardly different from the reasoning of the drug companies in the 1950s who said that since women with toxemia have hypertension and edema, they should be treated with a diuretic and a low salt diet, to eliminate water and to reduce blood pressure.

The physiological loss of sodium occurs when energy metabolism fails, as in diabetes, hypothyroidism, hyperestrogenism, and starvation. What these conditions have in common is an increased level of free fatty acids in the blood. Increased free fatty acids impair the use of glucose. The consumption of carbohydrate, like an increase of thyroid hormone, insulin, or progesterone, increases the retention of sodium; fructose is the most effective carbohydrate.[3]

The loss of sodium is often accompanied by the retention of water, reducing the osmotic pressure of the body fluids. The leakiness of blood vessels allows the extracellular fluid volume to increase, as understood in the standard definition of edema. However, when this fluid is hypo-osmotic, it will enter cells, causing them to swell. Cell swelling excites cells,[4,5] and can kill them if they are unable to produce enough energy to restore their original volume, by measures including the excretion of amino acids and potassium. Both low sodium (hyponatremia) and low osmotic pressure stimulate the adrenergic nervous system.

The increase of adrenalin, caused by a deficiency of sodium, is one of the factors that can increase blood pressure; if the tissues's glycogen stores are depleted, the adrenalin will mobilize free fatty acids from the tissues, which tends to inhibit energy production from glucose, and to increase leakiness. After I had read Tom Brewer's work on preventing or curing preeclampsia with added salt, I realized that the premenstrual syndrome involved some of the features of preeclampsia (edema, insomnia, cramps, hypertension, salt craving), so I suggested to a friend that she might try salting her food to taste, instead of trying to restrict salt to "prevent edema." She immediately noticed that it prevented her monthly edema problem. For several years, all the women who tried it had similarly good results, and often mentioned that their sleep improved. I mentioned this to several people with sleep problems, and regardless of age, their sleep improved when they ate as much salt as they wanted. Around that time, several studies had shown that salt restriction increases adrenalin, and one study showed that most old people on a low sodium diet suffered from insomnia, and had unusually high adrenalin. When they ate a normal amount of salt, their adrenalin was normalized, and they slept better.

It's very common for physicians who are aware of progesterone's "anti-aldosterone" activity to think that both estrogen and progesterone are responsible for the increased risk of sodium loss in women, especially

during pregnancy, but Hans Selye demonstrated that progesterone will normalize sodium retention even when there is no aldosterone at all, following removal of the adrenal glands. It is estrogen which is responsible for the dangerous loss of sodium.

The ratio of estrogen to progesterone—regardless of age or gender—is an important factor in regulating minerals and water, cell energy metabolism, and blood pressure. The ratios of many other regulatory substances (including serotonin/dopamine, glucagon/insulin, and aldosterone/cortisol+progesterone) vary according to the quality of the individual's level of adaptation to the environment. Improving the environment can shift the ratio in the direction of restoration, rather than mere survival.

Gershom Zajicek and his colleagues have demonstrated an organized renewal of tissues, in which new cells are born with the division of stem cells, and "stream" away from their origin as they mature, and finally are shed or dissolved. A few studies have demonstrated a similar kind of migration of new cells in the brain,[6,7] a process which differs by the absence of systematic dissolution of mature brain cells. While Zajicek has demonstrated the conversion of one kind of cell, such as a pancreatic ductal epithelial or acinar cell into insulin-secreting beta cells, other researchers have shown that after injury to the pancreas beta cells can be formed from glucagon-secreting alpha cells, as well as from other beta cells.

Stress, increasing the need for energy, increases the formation of cortisol and free fatty acids when glucose isn't available, and those—while they provide alternative sources of energy—interfere with the ability to produce energy from glucose. Free fatty acids and cortisol can cause the insulin-secreting beta cells to die. Glucose, and insulin which allows glucose to be used for energy production, while it lowers the formation of free fatty acids, promotes the regeneration of the beta-cells. Although several research groups have demonstrated the important role of glucose in regeneration of the pancreas, and many other groups have demonstrated the destructive effect of free fatty acids on the beta cells, the mainstream medical culture still claims that "sugar causes diabetes."

In the adrenal glands, renewing cells stream from the capsule on the surface of the gland toward the center of the gland. The first cells to be produced in a regenerating gland are those that produce aldosterone, the next in the stream are the cortisol producing cells, and the last to

be formed are the cells that produce the sex hormones, the androgens including DHEA, and progesterone. In aging, after the age of thirty, the renewal slows, but the dissolution of the sex hormone zone continues, so the proportion shifts, increasing the ratio of the aldosterone and cortisol producing cells to the layer that produces the protective androgens and progesterone.[8]

Even before aldosterone was identified, progesterone's role in regulating the salts, water, and energy metabolism was known, and after the functions of aldosterone were identified, progesterone was found to protect against its harmful effects, as it protects against an excess of cortisol, estrogen, or the androgens. New anti-aldosterone drugs are available that are effective for treating hypertension and heart failure, and their similarity to progesterone is recognized.

While stress typically causes the adrenal glands to produce cortisol, extreme stress, as described by Hans Selye, damages the adrenal cortex, and can cause the cells to die, leading to the death of the animal. There is evidence that it is the breakdown of unsaturated fatty acids that causes damage to the adrenal cortex in extreme stress. Although many factors influence the production of the adrenal steroids, arachidonic acid, even without being converted to prostaglandins, is an important activator of aldosterone synthesis. Adrenalin, produced in response to a lack of glucose, liberates free fatty acids from the tissues, so when the tissues contain large amounts of the polyunsaturated fatty acids, the production of aldosterone will be greater than it would be otherwise.

The continuing accumulation of polyunsaturated fats in the tissues is undoubtedly important in the changing relationship between the pancreas and the adrenal glands in aging. Aspirin, which is antilipolytic, decreasing the release of free fatty acids, as well as inhibiting their conversion to prostaglandins, lowers the production of stress-induced aldosterone, and helps to lower blood pressure, if it's taken in the evening, to prevent the increase of free fatty acids during the night. Aspirin increases insulin sensitivity. A low salt diet increases the free fatty acids, leading to insulin resistance, increasing free fatty acids in the blood, and contributing to atherosclerosis.[9–12]

The same factors that support or interfere with cellular renewal in the pancreas and adrenal glands have similar effects in the bones, skin, skeletal and heart muscle, nervous system, liver, and other organs. In every case, the local circulation of blood is influenced by both local and

systemic factors. The loss of control over the water in the body is the result of energy failure, and hypertension is one of the adaptations that helps to preserve or restore energy production.

Lowering inflammation and the associated excess of free fatty acids in the blood, and improving the ability to oxidize glucose, will lower blood pressure while improving tissue renewal, but lowering blood pressure without improving energy production and use will create new problems or intensify existing problems. After 40 years the medical profession quietly retreated from their catastrophic approach to pregnancy toxemia, but in the more general problem of essential hypertension, the mistaken ideology is being preserved, even as less harmful treatments are introduced. That ideology prevents a comprehensive and rational approach to the problems of stress and aging.

A Biophysical Approach to Altered Consciousness

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ORDINARY chemical and biological thinking tends to emphasize special functions at the expense of general and organismic processes. I want to suggest some of the ways in which "physical state" ideas can bring generality to the complex biochemistry of consciousness and behavior.

I use the phrase "physical state" to suggest that life, and its pathological and evolutionary modifications, can profitably be considered as a special "state of matter." The liquid crystalline state, with its various degrees of order, is a good example of another special state of matter. Living material is peculiar in being able to use external energy to increase its order without having to reduce its temperature; nerves and muscles, for example, consume ATP and CrP when they "fire," and they are able to return to their resting, sensitive state as long as energy is available. These active and resting states differ in various ways, such as preference for sodium or potassium ions, volume,[1] and even in the freedom and average alignment of their water molecules.[2,3]

These two states, active and resting, can also be characterized, respectively, as hydrophilic and hydrophobic;[4,5] as sodium-loving, and potassium-loving; as inefficient and efficient.[6]

The all-or-nothing impulse of a neuron is not the only known or plausible[7,8] mechanism of nervous communication. Nevertheless, all forms of cell conductivity are subject to modification by any process which shifts the equilibrium in either direction from the normal resting state—toward excessive "readiness," or toward incomplete restoration of the resting sensitive state. Russian biologists are most active in studying the changes that occur in tissue exhaustion[9]—e.g., increased dye uptake, decreased electrical conductivity—but Crile[10] and others several decades ago discovered some of the basic electrical properties of tissue related to consciousness.

If such tissue conductivity is a gross aspect of the kind of conduction which maintains our perceptual model of the world, we would expect a disturbed "state equilibrium," through its effect on conductivity, to alter our perceptions in general ways, such as spatial expansion or foreshortening.[11,12] Since such perceptual changes are common in depression,

mania, "schizophrenia," paranoia, delirium, etc., this "physical state" theory would predict that ionic and metabolic intervention would be possible to relieve those conditions. There is a long history of "resonance" models of consciousness, and some of them are highly relevant to this holistic and physical approach.[13,14]

There are many examples of gel hysteresis, in which a transition in one direction is easier than a return to its previous state. This seems to be what happens in the cornea after a prolonged riboflavin deficiency: even very high doses of riboflavin fail to restore its concentration in the cornea to a normal level, as if its solubility in the corneal gel had been reduced.

The monovalent alkali metal ions "bind" to themselves more water molecules as their radius becomes smaller, i.e., in the series rubidium, potassium, sodium, lithium. In this sense, lithium can be considered to be "super-sodium," and rubidium would be "super-potassium." Their affinities for cell proteins are apparently determined by their own radius and by the charge concentration of sites on the proteins.[15,16] The presence of these ions in turn stabilizes the conformation of the protein-water system in such a way that the charge concentration of the protein sites continues to favor those ions, barring the intervention of a stronger influence. These stronger influences may include powerfully adsorbed polyions such as ATP,[16] or certain changes in amino acids, or disturbed electronic conditions.[17] Glutamic acid increases the cell's ability to take up other amino acids, while glycine acts in the opposite direction;[18] glutamic acid also acts as a "cofactor" with ATP, probably sterically, in enabling the cell to take up potassium.[19] This steric function could account for the interference of synthetic (i.e., a mixture of levo and dextro forms) monosodium glutamate with brain development in rodents, and sometimes with nerve function in humans. Natural glutamic acid would be predicted by this theory to facilitate recovery of sensitivity in a depressed brain.

Lithium and rubidium have opposite influences on neuroexcitability, as predicted by this physical theory of the living state. Damadian[20] emphasizes the importance of this point, because "if one tries to explain these data in terms of conventional membrane pumps, one is at a complete loss to explain why lithium quiets the neuro-excitable state and rubidium enhances excitability."

The usual definition of a cell's "energy charge" is given in terms of ATP, ADP, and AMP,[21] with a high energy charge—an abundance of ATP—corresponding to what I am calling the resting state of "readiness." According to Szent-Gyorgyi[22] there is probably another sense in which cell proteins can be charged, namely, by addition to their "electron pool," which is a capacity of washed proteins to reduce large amounts of glutathione (discovered in 1925 by Hopkins; this capacity is what Racker has referred to in his cute phrase "nothing dehydrogenase"). Szent-Gyorgyi feels that this electron pool may provide the energy used to drive cell division. This energy seems to be derived mainly from glycolysis, which operates in the liquid phase of the cytoplasm. A related observation is that agents—e.g., estrogen—that promote mitosis also cause a proportionate increase in oxygen consumption and reducing capacity of whole tissue,[23] but that this capacity is lost if the cells are disrupted. This would suggest that the Hopkins electron pool is only a remnant of a larger and more delicately balanced pool, which can be kept in balance by draining electrons into oxygen as long as that is available; some pigments might serve as substitutes for oxygen in an emergency. Peroxidase and age pigment could catalyze this "draining" process.[23]

If such an electron pool is an integral part of the protein structure of the cell (Szent-Gyorgyi[22] has suggested the protein nitrogens as a likely site), then Szent-Gyorgyi's approach becomes a perfect complement to Ling's,[16] since the charge concentrations on the ion-binding sites of proteins are crucial factors in cell regulation in Ling's theory. It is well known that electron releasing or attracting groups have inductive effects through adjoining atoms, and Ling's view is that the strong ("cardinal") adsorbents can act through such inductive effects on adjoining charge concentrations. Szent-Gyorgyi also believes that these electrons could regulate the degree of protein hydration.[22]

The source of these electrons is likely to be NADH and/or NADPH, which are produced abundantly in the cytoplasm and which contain high-energy electrons (NADPH provides the energy for many biosynthetic reactions). For example, NADH and NADPH are the source of electrons for reducing glutathione, which in turn is in equilibrium with the SH groups of proteins.[23] Niacin is a component of these molecules that are so important in energy delivery. In a niacin-deficient animal, estrogen has no effect, so if estrogen is acting through its influence on the

electron pool, NADH and NADPH seem to be necessary for energizing that pool. Of course the biosynthetic function would also be damaged in a niacin deficiency.

The fact that large doses of niacin can often cure schizophrenia[24,25] suggests that in this disease the energy charge of neurons may be low. This would affect the ability of cells to retain certain ions and the known mineral changes that occur in schizophrenia[26] may be similar to those that appear in general stress reactions, though possibly with the brain being most affected. A low electron pool in schizophrenia might account for the claim that schizophrenics seldom develop cancer, since the cancer state, like other mitosis-favoring -states, presumably requires a very large or excessive electron pool. (The resistance of schizophrenics to virus infections, allergies, and histamine,[27] would suggest lower susceptibility to cancerization by viruses or irritation.) In the normal states, proteins would be "charged" only enough to function, bind water, etc., and then energy production would be limited. In a sense, the schizophrenic would be "too weak" even to produce cancer.

Szent-Gyorgyi[28] has shown that a given process can have opposite effects in different tissues, depending on whether that tissue is already above or below its maximum capacity to produce the particular effect. Recognizing that cells can have different degrees of structure according to their normal function and position in the developmental gradient, we should look for concepts that can combine generality with recognition of individuality, rather than grasping for undergeneralized answers such as "special receptor" theories.

Many people have suggested that pigments such as melanin may be able to function as electron acceptors, as an alternative to oxygen—no one has yet thought of a better explanation for the occurrence of pigments in the nervous system (e.g., the substantia nigra), in association with rapid mitosis,[29] e.g., melanoma and skin irritation, or in hormone imbalance or vitamin deficiency,[30] e.g., pellagra, Addison's disease, "melasma of pregnancy." We could imagine the pigment receiving electrons that "overflowed" from the electron pool, in case of a control error, or that leaked out of the pool, in case of structurally defective protein-gel systems. A phase shift of the cytoplasm toward "melting" would be the common event. Discontinuity of the proteins probably causes the low conductivity. The fact that abnormal pigmentation occurs in a niacin deficiency and in association with psychosis[31]

suggests that a metabolic or structural energy problem may be the key to both conditions. The observation that ascorbic acid with its high electron energy can be helpful in psychosis (Cott, ASA Publication) as well as in B-vitamin deficiencies has the same implication—ascorbic acid has both structural[30] and energetic effects. The electron donor potential of a substance has been successfully used to predict its effect as a hallucinogen,[32] and combinations of donor and acceptor substances induce muscle contraction[33] and may be involved in dyskinesias.[31]

Usually we think of both "error" and correction as being on the molecular level. However, control processes are likely to be of a physical nature first, followed by a chemical adaptive response. For example, if oxygen is physically restricted, the resulting lactic acid tends to restore the oxygen supply by causing vasodilation. Transmitter granules in nerve endings likewise are believed to be ruptured by physical changes in the cytoplasm, leading to the release of transmitter substances. Thus, we might look first for unusual functional states, such as stressed consumption of oxygen or glucose, or a nutritional block to such consumption, as provoking the release or synthesis of unusually high or low amounts of regulatory substances. Even vasodilators or vasoconstrjctors are ultimately regulators of the cytoplasmic "phase"; some hormones may do this more subtly, though. In this connection, it is interesting that a vasoconstrictor action has finally been demonstrated for LSD. The action of niacin as a vasodilator may be significant in its ability to block intoxication by hallucinogens (personal observation), as well as to block the symptoms of schizophrenia.

Schizophrenics typically have an abnormal serotonin concentration in their pineal gland. The pineal is rich in both serotonin and its N-acetylated, O-methy-lated derivative, melatonin, which has the function of concentrating melanin, making it seemingly disappear by withdrawing it from the extremities of the melanocytes. An interesting complexity is that the hormone is chemically closely related to the pigment that it regulates. The enzyme peroxidase, which is almost universally induced by irritation or stress, is involved in the synthesis of melanin.[31] The same enzyme can efficiently dispose of both electrons and oxygen.[23]

The pineal is closely associated with the optic thalamus and the reticular system, and is functionally involved in response to light, and is antagonistic to the gonads' production of sex hormones.[34] Its involvement in the visual system suggests it would be important in perception

and dreaming, and related to agents that either stimulate or suppress the dream-consciousness, such as LSD or alcohol.

A common item of folklore is that alcoholics are likely to be lightly pigmented people; sexual problems are often suggested, but usually are treated as an effect rather than a cause of alcoholism. Sensitivity and imaginativeness are frequently attributed to alcoholics. (Newsweek[35] reported successful use of lithium salts to treat alcoholism; this could be interpreted as acting to depress the "dream process," lowering excitability.)

Rat experiments[36,37] have shown that the pineal gland is involved in preference for ethanol: injected melatonin makes them prefer alcohol, as does keeping them in the dark. Removal of the pineal prevents this response to the dark.

It is well known that alcohol suppresses dreaming, usually for several days following intoxication, while the alcohol remains in the body. The body's "need to dream" is temporarily suppressed, but catches up later with a night or two of unusually intense dreaming. Continuous intoxication presumably builds up an increasing "dream pressure" that can eventually break through as waking dreams, or "delirium tremens." LSD works the other way, stimulating intense dreams even when awake, but causing a few dreamless nights when its direct effect wears off. (Para-chloro-phenylalanine, which blocks serotonin synthesis, not only interferes with sleep—especially R.E.M. sleep—but it causes rats to reject alcohol, and to become hypersexual[38]). The dream process involves greater conductivity through the head, whether it happens during sleep or when awake (my unpublished observations). This suggests that it corresponds to a high efficiency "resting" state.

It seems likely that human alcoholics, like the alcoholic rats, have excessive melatonin. This would account for the idea about their light pigmentation and possibly for an associated sex problem, since melatonin also suppresses the sex hormones.[34] Serotonin and reticular formation implants also have this suppressive action; male and female hormones may respond differently to serotonin and melatonin.[34]

Drinking would tend not only to suppress the dream consciousness (imagination may be a source of frustration), but may also antagonize the antigonadal action of the overactive pineal, though I don't know of any study that would indicate this—alcohol's occasional ability to increase sex hormone action is generally attributed to liver damage.

To the extent that psychosis is associated with excessive pigmentation, we might guess that it corresponds to a deficiency of melatonin; abnormal levels of serotonin (precursor of melatonin) in the pineals of schizophrenics could be interpreted in this way.

Stress, among its many effects, causes an increased synthesis of uric acid,[30] possibly as a useful adaptation, since uric acid levels correlate positively with mental activity and efficiency. However, uric acid can catalyze the oxidation of epinephrine,[31] and if this leads to elevated adrenochrome levels, it might interfere with cytoplasmic gel structure by acting on glutathione.[39]

Migrainoids typically have unusually vivid visual imagery and high electrical activity of the brain stem; a sudden drop in serotonin level is considered to be responsible for the swelling blood vessels that cause the pain, scotoma, etc. The travelling symptoms described by Reich and others may indicate that a certain mass of vessels exceeds the organism's vasoconstriction capacity; the demonstration that autonomic training can stop a migraine (by raising the temperature of the hands), the fact that sleep or orgasms can often end the symptoms, or that rectal stuffing can induce a headache, would be consistent with this idea. The "substitution" of bronchitis or piles (both involving vasodilation) for migraine would probably be conditioned by factors such as diet, activity, posture, etc. A high metabolic rate of any tissue will tend to cause reflexive vasodilation to maintain adequate blood circulation, as will relative starvation of the tissue, as in a riboflavin deficiency. In the migrainoid person, high brain activity, low blood sugar, and disturbed intestinal absorption may be interacting factors. Chernigovskii[40] has discussed some of the ways in which brain, blood sugar, and the intestine can interact.

The pituitary hormone, MSH (melano-phore-stimulating hormone), which causes darkening by dispersion of melanin, seems to act by way of interfering with glycolysis.[41,42] High pH and hypo-osmolarity[41] can also cause dispersion, which suggests that a phase transition (gel to sol) is involved. Kinosita[43] has reported exactly this gel-sol transition and has also demonstrated that the pigments seem to follow electrical gradients within the cell.

The idea of an altered state of the protein-water system makes it easier to see the darkening event, pigment dispersion, as a single process:

deficient melatonin, excess MSH, deficient niacin, or irritation, would all promote the low conductivity, low efficiency, anti-dreaming state.

During exhausting fevers and after drinking too much, I have experienced a defective kind of dream, a kind of analytical, verbal delirium, in which one word only leads to another word. In place of fluid and integrated imagery, there was just a kind of fizzly yellow, or swarming orange, activity. Mental satisfaction becomes impossible in that state. (Green and blue usually seem to be suppressed in that kind of state.)

Since I believe mental imagery is the real, working structure of language, I think a related kind of damage to the dream system, or dream metabolism, would account for the peculiar nature of "schizophrenic" verbalization. The damage would be both energetic and structural and would act by an effect on tissue conductivity. (An important difference between the cancer state,[6] and schizophrenia, on the cell level, would be that cancer depends on glycolysis, while glycolysis is specifically depressed in schizophrenia, according to this view.)

This theory, unlike others used as a basis for Orthomolecular psychiatry, offers a great range of substances that may be used simultaneously and possibly provides a better and more general basis for understanding synergisms (such as Ling's ATP-glutamate-potassium interaction). It specifically opposes the premature assumption that any particular metabolic error is genetic and proposes instead the investigation of environmental factors (including the uterine environment) that could alter the physical state of the cytoplasm. The observations of poor muscle tone in very young infants who later become schizophrenic has been used to argue for a purely genetic origin, but it could as well reflect a bad uterine environment, such as could be caused by an inadequate placenta.

Implied Theraputic Approaches

This biophysical theory argues that altered consciousness (and the behavior it produces) is a question of both bioenergetics and "biomicrostructure," and implies that a therapy should attempt to create the desirable state of structure and energy by intervention at crucial—and possibly numerous-points.

If it is possible to introduce ATP directly, its use would be suggested by the theory, since it is one of the central points in both energy

metabolism and structure. Creatine phosphate, which is in equilibrium with ATP, might be an alternative way of raising ATP concentration since it is at a higher energy level and would not introduce additional adenosine, thus allowing a higher ratio of ATP to AMP, if not an absolutely higher concentration of ATP. ATP has been found to improve the functional state of the brain (vestibular analyser) when used with Pyridoxine, increasing its stability and shortening postrotatory nystagmus[44] Also, ATP promotes healing of corneal wounds at high altitudes, when applied locally with 4-methyluracil.[45] Since ATP hydrolyzes rapidly in blood, it might achieve these effects partly through vasodilation. Recent in vitro studies show that ATP prevents leaking of enzymes and other proteins from cells (Science News, 1974).

Other "orthomolecules" besides niacin would, according to this view, include potassium, magnesium, vitamin E (improving oxygen supply, facilitating cell retention of proteins, and even, according to Matusis,[46] increasing ATP content), L-glutamic acid, inositol (stabilizer of cells and proteins against denaturing or "dehydrating" influences[47]), the other B vitamins, vitamin C, and anabolic steroids (e.g., testosterone, progesterone, ginseng, eleutherococcus) to promote protein synthesis and retention of potassium and creatine and ATP. Progesterone may be particularly important in female schizophrenics, since it commonly seems to promote emotional stability and even has an anesthetic function in large doses.[48]

Vitamins A, E, C, and B_2 either mimic or potentiate testosterone to some degree.[49] I am currently investigating the function of folic acid in allergic, immune, and perceptual processes.

The electronic aspect of the cell's energy charge suggests that cysteine or reduced glutathione might be desirable, especially if there is evidence that glutathione is being destroyed by something like adrenochrome. (Sulphydryl blocking can impair glycolysis, as can a niacin deficiency.) The theory of donor-acceptor interaction might eventually lead to a specific understanding of the "electronic leak" and how best to intervene, though it might not be such a discrete problem as some theorists have hoped.

The glutathione peroxidase which is released when mitochondria swell[50] might be involved in the "electron leak," and so things which cause uncoupling of oxidative phosphorylation and mitochondrial

swelling, such as unsaturated fatty acids[51] should probably be controlled in the diet.

Since the normal person has sharp diurnal cycles of brain activity (reflecting a proper concentration of the "brain" amines) and many psychotics have flattened cycles, involving disturbed sleep as well as disturbed waking consciousness, cyclic light stimulation of skin and head might be desirable to support regular cyclic activity of the pineal gland and brain. This would also tend to increase sex hormone production by the gonads.[34] The brain's "background activity" might have what in the heart is called the "staircase" effect, in which structural readiness seems to leak away if the tissue doesn't become active often enough—"function builds structure, and structure produces function."[22]

"Rhythmotherapy," the imposition of normal rhythms, is being done with the apparatus called "LIDA," which produces pulsed light, sound, and UHF currents, and a breeze on the face.[52]

Hyperbaric oxygen therapy has been used in relieving psychotic symptoms,[53] but this doesn't seem appropriate for creating lasting improvement. The opposite condition, i.e., high elevation, has caused lasting improvement in psychosis (Mir-rakhimov, 1972) and many somatic and psychosomatic conditions, and the mechanism (according to the animal studies of F. Meyersonet al., 1972) is the adaptively increased number and efficiency of mitochondria in the brain, resulting in improved learning ability. Also, MAO activity decreases at high elevation while respiratory effectiveness increases.[54]

In a pharmacological approach, reduced expenditure of glycogen, ATP, and creatine phosphate,[55] combined with increased protein synthesis[56] and increased resistance of cells and organisms to stress, can be achieved with ginseng, eleutherococcus, and 2-benzyl-benzimidazole,[57] used singly or in combination. Piracetam, an analog of GABA, improves learning, increases resistance to toxins or oxygen deprivation, and increases bilateral symmetry of function in the cerebral hemispheres.[58]

The importance of improving protein synthesis is implied by the observation that serum from schizophrenics inhibits protein synthesis in rat cerebral hemispheres, hypothalamus, and cerebellum.[59]

Several people[60] have suggested an identity of acetylcholine, epinephrine, and serotonin "receptors," and this structural-energetic theory similarly would suggest that "specific receptor" psychopharmaceutical approaches lack a proper physiological basis. But studies of

psychoactive agents can contribute to a general understanding of cell and brain function and can possibly support an Orthomolecular approach. For example, when excessive cholinergic activity is involved in nervous dysfunction (and excessive acetylcholine can block cholinergic synapses[61]), cholinolytic cell stabilizers (e.g., acetylcholine or tetramethylammonium with the adamantyl radical substituted for the N-methyl group[62]), might be used to stabilize nerve function while actual repair processes occur under Orthomolecular therapy. The adamantyl radical is also useful in treatment of Parkinsonism and viral infections[63] again suggesting a general biophysical structuring effect, as in cholinolytic processes. The "Pavlovian dose" of caffeine which produces sedation is very small and probably acts by increasing the degree of structuring of cells; larger doses, which would promote an "adrenergic" state, might intensify the symptoms of schizophrenia or alcoholism. The cholinergic and muscarinic drugs (e.g., prostigmine) might shift the nervous balance in the right direction if the cholinergic synapses aren't blocked by excess acetylcholine.

The Russians have two electronic techniques that may serve as alternatives to ECT and which may in fact give some insight into the effects of ECT on the brain. Electrosleep (produced by 5 Hz to 100 Hz pulses, with peak current of 5 mA to 8 mA applied to the eyes—negative pole—and mastoid process—positive pole) has been used in treating "functional disorders of the CNS," autonomic and endocrine functional disorders, etc.[64] High frequency (5000 Hz to 6000 Hz) currents have been found to stimulate the brain.[65]

In embryonic muscle cells, when the "depolarizing fast acetylcholine receptors" are blocked by snake venom, then the cell's "slow polarizing acetylcholine receptors" are revealed[66] This type of receptor may be responsible for the "trophic" influences which maintain high polarization and which seem to be involved in such things as the "Bowditch staircase." Electrical stimulation may act on similar "receptors" in neurons.

Vitamin B_6 is a coenzyme in carboxyl-ation reactions and as such is involved in the synthesis of serotonin from 5-hy-droxy-tryptophan, and also in the formation of GABA (gamma-aminobutyric acid) from glutamic acid. In the "resting" state, cell water seems to be more orderly, as if it had a lower "structural temperature." Some enzymes are inactivated by cold and presumably would be inactive in the resting state. GAD (glutamic acid decarboxylase) has been found to be among these peculiar

enzymes, and this is the enzyme which decarboxylates glutamic acid, producing GABA. GABA has been shown to be a mediator of nervous inhibition on the basis of several criteria, including heightened GABA liberation in sleep and near-sleep.[67]

This would seem appropriate if the physical state of cell water is participating in brain regulation. During brain "activation" or exhaustion, this enzyme should become more active, producing more GABA and presumably thereby promoting rest and restoration. Since hydroxylamine is an inhibitor of GABA degradation, it would be interesting to see what effect it has on psychoses, though it may be too toxic to be practical; the same might apply to hydrazine, which is used with considerable success in inoperable cancer and often induces sleep as well as preventing cachexia. It raises the level of ATP systemic ally. Injected GABA is usually considered to enter only the fetal or infant brain, because of the "blood brain barrier" of the more mature organism. However, Nasonov and his students have shown that many kinds of stress will eliminate the barrier and that it can be interpreted as a physical state of the neuron, governing solubility. This suggests that GABA itself may be able to enter the brain and exert a beneficial inhibitory action if the brain is in a state of exhaustion from stress.

Another enzyme that should be investigated from this point of view is NADase, since it too shows what may be a sensitivity to structure: in cell homoge-nates, it is sufficiently active to destroy NAD and thus stop glycolysis at the triose phosphate stage;[29] it is inhibited by nicotinamide, but is also relatively inactive in the intact brain, at least in the intact non-schizophrenic brain.

Magnetic fields presumably act biologically by acting on the structure of water, and Kholodov has established that a continuous sinusoidal magnetic field has a sedative and inhibiting effect, modifying the EEC and raising the level of GABA in the brain.[68] The activity of oxygen increases in magnetically treated water,[68] so there might be a direct effect on energy production.

Since DMSO has been used successfully for treating mental retardation, with removal of cataracts as a side effect, its effect of "structuring" water, or lowering its "activity" according to a Soviet study, and of promoting oxidation of glucose by quinone (my unpublished observation) suggests that it might improve the function of nerves and other cells by promoting the desired high energy state.

During an epileptic seizure, a localized vascular "blanching" has been observed in the exposed brain. Since vasoconstriction occurs in the brain when the concentration of carbon dioxide is low, such a spasm might occur when metabolic inefficiency interferes with the production of carbon dioxide. Thus epilepsy and schizophrenia might benefit from similar treatments. This theory suggests that we should look for more general mechanisms in known therapies: for example, the ability of Dilantin to lower insulin levels could improve the supply of glucose to the brain.

One of the older therapeutic uses of niacin is in the treatment of "trench mouth," which is a reaction to stress,[69] though a protein deficiency is also probably involved. Since the gums are responsive to many agents (including Dilantin and cigarette smoking) and are easy to inspect, they may provide an additional means for following the course of recovery when schizophrenia is being treated with niacin.

A Holistic Physiology of Memory

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WHEN we think of memory, it is customary to use concepts such as "storage," "reservoir," and "trace," and to look for ways in which the "trace" might be integrated with "sensory input" and "motor output." I want to suggest that these concepts are derived from a particular philosophical approach which is deeply embedded in "western civilization," but which is probably not able to deal appropriately with questions such as consciousness, memory, and organism.

Abundant experimental evidence has shown that perception is an active process. Yet nearly everyone seems satisfied to diagram "sensory input" and "motor output." Where is the sensory output in the typical diagram of a functioning organism? It is forgotten, generally, because the passive reservoir of memory can do nothing but receive sensations and store them until they are drawn upon for motor activity. But what could sensory output consist of? How could consciousness go out? This odd question is normally avoided by avoiding the discussion of consciousness—it is said to be beyond the scope of science, etc., while "input, storage, output" are simple, manageable concepts. Those concepts are useful in the analysis of a typewriter, but a typewriter doesn't have a fundamental selectivity of the messages it receives. Since perception is an active process, it is necessary to consider sensory output, or how consciousness "goes out." This is not mere muscular orientation, and it involves many distinguishable levels: thresholds are adjusted, patterns are sensitized, and the whole perceived world-space is finely adjusted to the flow of perceptions.

There have been various demonstrations of structured, meaningful antidromic impulses on the optic nerve. This is an output through a sensory channel, and it powerfully determines perception. Passive movement of the eyeball creates the illusion that the visual field is moving, while an intentional movement of the eye or head involves a coordinated movement of the perceived model of space. This perceived model of space, and its ability to jump in synchrony with expected changes of perception, is another aspect of the active consciousness. It is this active model of the world which Anokhin called the "acceptor of action." Once we recognize this active perceptual model, we commit ourselves

to Anokhin's "completion of the reflex arc," the feedback principle in which motor activity is inseparable from "image," "sense," intention, and consciousness.

At first, the imbalance between many sensory nerves to the brain and few motor nerves from it suggests that we sense more than we can do, but there is normally not any problem with refining muscular activity to suit the situation. It is the sensory "output" system which provides the means of orientation and control. This is equivalent to the view of Pavlov's followers that the cortex is a "sensory" system, even when it is regulating the musculature.

It has been suggested that the position of the eyeball is perceived largely by an awareness of the impulses that are being directed to the eye muscles. If this is true, it is only a "simplified" case of what Anokhin presents as the general nature of organismic control. The two elements, active perception and perception (feedback) of movement, constitute a picture of the active consciousness, of the active organism. The imaging cortex fits the organism to the environment, both perceptually and motorically.

At the Seventh World Congress of Cardiology (Buenos Aires, September, 1974), there were about a dozen reports by Western scientists relating to the role of nerves in heart disease, but previously this factor was considered important only by the Russian Pavlovians. Pavlov developed the concept of cortical control of trophic processes in all tissues, although the study of nerve trophism was already established in Russia in the mid-nineteenth century. Bykov (1957), Palladin (1959), and Filatov (1957) are among those who have studied the influence of the cerebral cortex on tissue biochemistry. Nerves also have trophic influences on other nerves. Nerve trophic influences are coming to be accepted by Western physiologists (e.g. Brown, 1974). There is probably no consciousness without a body component, a feeling tone, an orientation, a trophic influence.

In this context, it is interesting to remember the old physiological demonstration of the mammalian "nerve net," in which the anal sphincter of an anesthetized cat is attached to a recorder—students are invited to think of a stimulus, such as tickling the ear, to show that every stimulation will modify the tone of the muscle.

Our perceptions are modified by the tone and balance of our autonomic nervous system. Certain gestures and postures modify our

perceptions and recollections. Lying down goes with a certain style of thinking, standing, with another style. Some personality types move their eyes to the left while thinking, others to the right; blinking and rolling the eyes seems to facilitate another kind of mental process. Blinking is commonly used to "erase" eidetic images. These physiological events are closely related to our "getting a perspective."

Wilder Penfield found that electrical stimulation could promote recall. The memories could be repeatedly recalled with repeated stimulation of the same point. Pavlov spoke of a focus of learning, and the Russian concept of a dominant is also thought of as a centering in the brain. The holographic idea of brain function also implies the importance of "perspective." I think we can work from the organismic nature of this perspective, or "field," or orientation, down to the cellular and chemical level, but it would be very hard to go in the opposite direction.

When we talk about perspectives, we aren't making a distinction between perceiving and remembering. Similarly, learning and perceiving can both be thought of as active, constructive processes. Of course, perceiving something familiar is not the same as perceiving something new, which requires learning or discovery. The difference can be seen in terms of the idea of development, in the biological sense. Growth, differentiation, and integration are included in this concept. There is also an implication of evolution and generalization. The idea of "storage" can be fully replaced by this more phenomenological, experiential, empirical idea.

A common implication of the idea of "storage" is that memories must be inert while in storage; the organismic approach suggests that various degrees of integration can exist. Some of the organism's developmental processes may reach dead ends, become isolated, irrelevant and inert. But if the organism is making use of most of its experiences, there will be fewer dead ends. Once entering this complex world of interlocking meanings, we can't leave it without undergoing something like a developmental regression. And to the extent that it is present, the question of "recall" disappears or at least changes its form.

If we consider some of the recent historical reasons for requiring the ideas of recall, storage, and retrieval, it might give us some suggestions for studying the holistic aspect of memory.

A few years ago, it was common for psychologists to claim that there was a tremendous "information reduction" in visual perception, because, for example, only about six simultaneously presented points seemed to be the maximum that could be recognized instantaneously. The existence of eidetic imagery has always made this a foolish position, but it was only recently that many behaviorists were made to recognize this by studies of people with eidetic imagery, using computer generated images composed of millions of random dots. Holding as they did, the dogma of "tiny input, tiny output," they were forced by the fact that many people know many things, to conclude that the tiny stream of input was stored in a fairly large black box.

Now we just can't avoid knowing that the channel of visual perception is very large: ordinary people can, for example, recognize at a glance which photographs in a series of 2000 are repeated. We also have to grant that perception is active: the perceiver brings himself and his world to bear on the thing perceived. The "very large input channel," therefore, is made even larger by the activity which recognizes, which "intends," which gives meaning. In a normal continuing situation, this amplification by recognition is momentary and continuous; in a typical, sporadic experimental arrangement it may almost disappear, or appear later so that it appears to be something separate. When we see that perception is rich and active, and constitutes the phenomenological or empirical being of the organism, we aren't forced to ask where something is "stored" when it isn't explicitly present. That question, "where is memory stored?," is somewhat like the question, "where is the organism stored when it is quick-frozen?" In fact, at that time, the organism exists only potentially, since its future functioning depends on the circumstance of successful thawing, which is a reconstruction of the physiology. Another example: when an organism is eating, where is its mating behavior? Is it in storage? Only in the sense that the organism developed its sexual organs, its nervous system, etc. at some earlier time—and eating is, in fact, a necessary preparation for mating and other behavior. Recognizing the full nature of the organism, we can say that one behavior is explicit, while others are implicit.

A child develops its sexuality, its style of movement, its language, its visceral peculiarities, its skills, its image habits, and other ways of dealing with the world. If it is idle to talk about our "sexual reservoir"

which "stores mating" while we read or eat, then it is idle to talk about a reservoir of words or images.

Many geneticists are talking about manipulating, transferring, and storing DNA, and the assertion is commonly made that the DNA contains "all the information in the organism." It has been known for decades that cleavage patterns, which determine important biological traits such as which phylum the organism belongs to, are governed by the cytoplasm independently of the transplanted nucleus. Many other experiments show inheritance of structural properties of the cytoplasm, without involvement of "genes." So it is false to assert that DNA contains all the information needed to make an organism. Unfortunately, this mistaken genetic thinking is taken as a paradigm by many of the people who are thinking about memory molecules and information storage. The "reservoir" tends to be equated with molecules which are known to transfer learned behavior. There are probably many factors which could transfer learned behavior. The quick decay of the transferred learning suggests that the transferred molecules are not all that is necessary to establish or integrate that behavior. But even if a perfect chemical transfer method is achieved, it won't be an argument for the existence of a storage system distinct from the input system. To use an analogy, we could imagine that technicians could eventually restructure the cytoplasm of a flatworm egg into the cytoplasm of a snail egg, by transferring essential parts of the snail egg and placing them appropriately. In this case, we see that being and functioning are equivalent, and nothing is gained by talking about storage of the snail egg's function.

I think that by criticizing some of the empty and misleading formalisms in this way, we can clear the way for a better understanding of the real physiology of memory, of memory transfer, and of brain function in general.

A New Approach to Detoxifying

Townsend Letter for Doctors, January, 1989

Ernest Krebs, the inventor of the laetrile cancer treatment, compiled some interesting facts about cancer metabolism. Noting that cancer cells are typically fairly deficient in the enzyme rhodanese, which protects cells against cyanide poisoning if the dose isn't too high, he theorized that cyanide might selectively kill the relatively unprotected cancer cells, especially if the dose could be concentrated near the cancer.[1]

While amygdalin releases a large proportion of its cyanide in the bowel, his original laetrile, the glucuronide form, should liberate its cyanide largely in areas of inflammation or injury, including cancers.

Although cancer cells have a low level of rhodanese, they typically have intense glycolytic metabolism which compensates for their respiratory defect. Otto Warburg and Dean Burk showed pretty decisively that "defective respiration" exists in all of the cancers studied.

Maybe we can see a different meaning in the same facts.

What if the respiratory defect that was so carefully documented by Warburg and Burk is the result of damage to the detoxifying rhodanese enzyme? If cyanide is a general threat to respiration, a deficiency of rhodanese would allow it to damage respiration, and this, according to Warburg, should lead either to cell death or, if the cell can adapt adequately, to the production of cancer.

Rhodanese occurs in all animals, and seems to be localized inside the mitochondria. Although it does handle some other sulfur reactions, its basic function is thought to be the elimination of cyanide, by the addition of sulfur, forming thiocyanate. Thiocyanate is fairly non-toxic, though it can be broken down into cyanide again, and it does have a significant anti-thyroid effect.

Herbivores eat many plants that are rich in cyanide-releasing compounds, so it is logical that they should be equipped with rhodanese. But carnivores are not exposed to these toxic vegetable products, so it is hard to explain why they have the enzyme. The fact that serum albumin, which has many detoxifying functions, carries sulfane sulfur, the form which is used by rhodanese to react with cyanide, supports the idea that rhodanese is involved in the elimination of cyanide.

People who smoke or eat significant amounts of plant material are exposed to cyanide, but the fact that the rhodanese enzyme exists in all animals, whether their diet includes "cyanophoric" compounds or not, suggests that we might want to consider other possible sources of cyanide.

People studying lipid peroxidation in liver cell extracts noticed that carbon monoxide was being produced. Many people have observed that stressed cells emit ammonia.[2] There are industrial processes which use ammonia and carbon monoxide to produce cyanide, using a metal as catalyst.[3–5] Since carbon monoxide binds to metal atoms, it might be held in a form which reacts easily with ammonia. Then during stress, which causes both lipid peroxidation and ammonia formation, rhodanese would be needed to protect the respiratory cytochromes from the cyanide, which would otherwise inhibit respiratory energy production, and other processes involving the cytochromes. Within the mitochondria, a cytochrome P-450 converts cholesterol to pregnenolone. The loss of both energy and steroid hormones would have major consequences. Outside the mitochondria, many other cytochrome functions will be inhibited; other types of enzymes would also be inhibited.

Another possible source of cyanide would be bacteria in the intestine; methane and ammonia are other possible starting materials for making cyanide. The urea cycle itself, inside the mitochondria, is a conceivable source.

Even if dietary plant material turns out to be the main source of cyanide, it is important to be able to eliminate it efficiently.

When flowers of sulfur is taken orally, some of it becomes available for use in the rhodanese system. It might be less irritating and more effective to use a form of sulfur which is chemically more available, namely thiosulfate. (My thoughts on light removing carbon monoxide from cytochromes led me to think about photography; sodium thiosulfate is used to clear the photographic emulsion, removing the silver which was not exposed to light. In that sense, its activity as a reductant is equivalent to light's action).

In acute cyanide poisoning, a large dose of sodium thiosulfate (12 g) is injected rapidly; it is poorly absorbed when taken orally. I decided to try small oral doses, about 50 mg. a few times per day. It has improved my tolerance for chocolate and wheat, which I still reacted to in spite of using pregnenolone, which was permitting me to eat many other foods

that earlier would have caused migraines and asthma. Pregnenolone seems to stabilize the cytochromes physically, while rhodanese (with sulfur) restores their chemical activity. Some druggists still sell sodium thiosulfate as a treatment for skin diseases. It has been used to treat arthritis, which would be logical if it is able to increase formation of pregnenolone and the various steroid hormones.

Since very high levels of cortisone destroy the detoxifying cytochrome enzymes,[6] the use of thiosulfate—to restore any of the remaining cytochromes which might be blocked by cyanide—would seem to be appropriate as part of an anti-stress approach to disease. As far as I know, it hasn't been tried as part of cancer therapy; improving a cancer cell's viability might, as many people believe, reduce its virulence, but it might just make it a more energetic cancer cell.

A Physiological Approach to Ovarian Cancer

EnCognitive, January, 2010

SEVERAL years ago, George Crile, of the Cleveland Clinic, observed that his clinic had removed only 11 thyroids that year, and that they had done more than 5000 thyroidectomies annually in the 1920s. The reason for the change was that they found that there was rarely any reason to remove the gland; even thyroid cancers of most types could be controlled safely by using a thyroid supplement, to reduce the growth-stimulating action of the pituitary hormone.

Since many physicians still believe that destruction of the thyroid gland, by radiation or surgery, is an appropriate treatment for thyroid disease, it isn't surprising that there is so little attention given to the possibility of physiologically controlling the more aggressive ovarian cancers. The recent report that ovarian cancer is more common among women who have taken gonadotrophins, to promote fertility, will probably bring increasing attention to the physiology of ovarian tumors.

Around menopause, the pituitary gonadotrophins increase. Menopausal estrogen treatment shouldn't be called "estrogen replacement therapy," because the amount given is typically about 15 times higher than occurs in younger women. The reason for the use of such high doses is that the dose is increased until the pituitary gonadotrophins are suppressed. The reason for the menopausal increase in pituitary hormones is that the nerve cells which regulate their secretion have been killed or desensitized by their past exposure to estrogen; it is their reduced sensitivity that requires the very large doses of estrogen to suppress secretion of the gonadotrophic hormones.

Clonidine (normally used for high blood pressure) can be used as a skin patch, to control menopausal flushing; progesterone and DHEA prevent osteoporosis. After those issues have been taken care of, the question of pituitary hyperfunction should be considered, in relation to preventing ovarian cancer. (Combinations of safe substances including progesterone and naloxone can probably be worked out empirically.) A variety of other possibilities exist, including Gonadotrophin Inhibiting Substance, and antagonists to the specific gonadotrophin release hormones. Normalizing the menopausal gonadotrophins would have far-reaching effects, possibly improving the immune response.[1]

For years, it has been known that nuns have a high incidence of ovarian, breast, and endometrial cancer. Women who have children, or who take oral contraceptives that might suppress ovulation, are believed to have a lower incidence of ovarian cancer because of reduced exposure to the gonadotrophins. (Though cancers of liver, breast, and other organs are reported to be more frequent among pill users; prolactinomas seemed to become epidemic after the pill was introduced.)

Normal factors in the physiological control of the ovaries include an interaction between the thyroid and the gonadotrophins; the combination of hypothyroidism and stimulation by gonadotrophins can cause ovarian cysts to develop. Small amounts of estrogen can increase both FSH and LH, and large amounts of progesterone decrease both FSH and LH.[2]

If ovaries are removed from their normal location, and transplanted into the spleen, so that their secretions go directly to the liver where they are inactivated, they produce tumors because they are subject to "hypersecretion of gonadotrophic hormones."[3–5] Other experiments support the idea that ovarian tumors develop from excess pituitary stimulation. For example, removal of one ovary was essential to produce a tumor in the other ovary even after it had been irradiated.[6] Similarly, no tumors developed in irradiated ovaries transplanted into other mice, irradiated or not, as long as they had their own ovaries, which kept the pituitary functioning normally.[7]

Progesterone and estrogen "receptors" can be demonstrated in some ovarian tumors, and by analogy with breast and uterine tissue, in which progesterone generally retards cell division and estrogen stimulates it, hormones have been investigated as possible therapies for ovarian cancer. Although *in vitro* studies show that there might be a direct action on the tumor cells,[8] the reports of positive responses in patients treated with progesterone or synthetic progestins[9–11] are more interesting, since the most logical approach involves normalization of the pituitary gonadotrophins.

If it is true that a "deficiency" of the so-called "essential" fatty acids suppresses gonadotrophin secretion,[12] then a diet lacking those estrogen-promoting[13] substances should be both protective and therapeutic for ovarian cancer (assuming that the results seen with progestin therapy are produced by gonadotrophin inhibition.) If our purpose is to delay the menopausal rise of the gonadotrophins, then it is interesting that

lipid peroxidation of polyunsaturated fatty acids (which increases with age) can be intimately involved in loss of progesterone forming ability by human steroidogenic tissues.[14] That is, aging decreases the ability of certain brain cells to inhibit the pituitary gonadotrophins, and it also tends to decrease the steroidogenic tissues' ability to produce the regulatory steroids.

After menopause, estrogen is produced less by the ovary than by other tissues, including fat cells. Breast cancer cells can produce their own estrogen. This means that estrogen is one of the "cancer hormones" which, secreted by the tumor, promotes the growth of the tumor and also has a systemic pro-cancer action. Ovarian tumors, too, can cause great systemic hormonal imbalances, which should be investigated routinely in a physiological approach to the disease. After menopause, estrogen is largely produced by conversion of "androgenic" steroids from the adrenal glands. It would be desirable to be able to inhibit the conversion of the adrenal steroid precursor to estrogen. Newton, et al.[15] showed that progesterone inhibits the conversion of the precursor to estrogen, and P.K. Siiteri showed a similar effect for thyroid hormone.

A diet low in polyunsaturated fats facilitates thyroid hormone secretion, transport, and tissue response to it, and would minimize the stress-related or age-related inhibition of progesterone formation by lipid peroxidation. Vitamin E and vitamin A also protect against lipid peroxidation, and vitamin A is specifically involved in progesterone synthesis. Vitamin A also has a variety of anti-estrogen functions,[16] that are often considered to be relevant to protection against cancer.[17–19]

All of these dietary and hormonal approaches to normalizing the pituitary gonadotrophins and controlling ovarian cell division are things which also tend to optimize the immune response. A slight deficiency of iron is probably protective against cancer, since there are several ways that iron can promote cancer, apart from its role in damage to the immune system and the steroidogenic system by lipid peroxidation.[20,21]

A Revolution in Physics

Multidisciplinary Research, Volume 4, Number 37, 1976

NIKOLA Tesla was aware that the earth has a high negative electric charge; he felt that going to high mountains, where the charge tends to be more concentrated, stimulated him mentally. It is now generally believed that the sun, too, has an excess of electrons. (H. C. Dudley demonstrated that the earth's charge could be used to make small rockets reach much higher altitudes.)

In spite of experimental evidence, this "electronic background" was conceptually hard to accept—some people still prefer to think that the observable charge gradient results from a source of positivity in the high atmosphere.

Electrons are relatively easy things to grasp, in a technical sense and in an intellectual sense—they have a high charge in relation to mass, and so flow easily, and are very useful. Nevertheless, the idea of a charged earth was hard to accept.

If there were uncharged electrons, they could be even more abundant, yet harder to detect. It has been proposed (Dudley, 1963, 1972) that there are several types of uncharged particles, including "neutral electrons," forming a "neutrino sea." The neutrino was not notoriously hard to detect, even when it was necessary to assume its existence to account for the recoil energy of a decaying atom.

In this century, two major ideas have been ruled out as general interpretive frameworks in physics: mechanistic or deterministic causality, an ether which serves as a medium for propagation of electromagnetic radiation.

DeBroglie (1959), Bohm (1959), and Dudley (1971) are among those who have more recently proposed a need for a "sub-quantic" medium. Dudley has elaborated the assumption that the medium is a "neutrino sea," with great success.

He was able to use it to account for the Fitzgerald-Lorents contraction. It is interesting that the Fitzgerald-Lorentz idea was first introduced to justify keeping the ether theory.

He predicted (Sept., 1972) results like Anderson's discovery of anomalous nuclear decay rates (Nov., 1972) when he postulated that

> *populations of nuclei which are now considered to exhibit spontaneous decay at a constant logarithmic rate, consist of units each of which is a linear resonant system. Parametric excitation of such a unit by an energy input at some critical level or rate may cause the system to react... ...with such a model there would be no necessity of assuming acausality in describing the "decay" of nuclei or particles.*
>
> *Dudley has warned that these new ideas regarding nuclear stability, if true, will invalidate the present AEC beliefs about reactor safety, etc.*

My involvement in this subject relates mainly to my view that biological processes are largely governed by crystal-like states of tissue water. Because of my familiarity with Polanyi's book, Personal Knowledge, I considered the applicability of his adsorption isotherm (1914) to biological ordering processes. Among other ideas I was considering as a possible guide to ordering processes was N. A. Kozyrev's proposal (about 1965) that time, which he had been viewing as a cosmic source of meg-entropy (lunar vulcanism, 1959; planetary asymmetry, 1964) might in some way be utilized by organismic forms. It was only recently that I read Polanyi's later (1920–25) scientific work on crystals and chemical reaction energy, and realized that his scientific work had been guided by a holistic principle, just has his more recent philosophical thinking is. As I presently understand it, his "mechanism for holism" was very similar to the "energy source and sink" that Dudley understands to be a neutrino sea.

A 1971 newspaper report about Anderson's experiments with monomolecular layers of radioactive chemicals aroused my interest in the likelihood of "new" kinds of surface, crystalling, and adsorptive forces or processes.

In Personal Knowledge, Polanyi had told the story of conflicting interpretations of the Michelson-Morley experiment. When Dror Sadeh's experiments were reported, showing, for example, a "red-shift" between locations on the east coast of the U.S., it seemed pretty obvious that either "time" (cesium clocks) or radiation (radio waves and light from stars) behaved in ways not acceptable to conventional theories.

When I heard of Dudley's objection to the Rafele-Keating experiment (which was claimed to verify the clock paradox of relativity), and to other

current dogmas, I asked him about the possible relation of crystals to the neutrino sea, and he indicated that he had predicted their interaction with phonons and rotons in crystals. This is where a "physical" theory becomes obviously relevant to organisms and their highly ordered water structures.

Dror Sadeh's clock seemed to slow down following sunrise and moonrise. Frank Brown had earlier found that hermetically sealed potatoes and oysters showed metabolic changes at sunrise and moonrise. Several Soviet biologists have argued that some kind of "radiation" other than electromagnetic is necessary to explain such biological sensitivity. A "sub-quantic medium," influences by events in the solar system, would be a conceivable explanation.

Bandyopadhyay and Chaudhuri have shown how the neutrino sea can account for gravitational attraction:

> *A body falls toward the earth because the charged particles of which the body is composed tend to move into a region where the dielectric constant is greater. Thus an electromagnetic interpretation of gravitation is obtained (1971).*

Bandyopadhyay and Chaudhuri also observe that "the variation of the neutrino energy density can be related with the evolution of the universe," though such variation is not an essential feature of their (1971) theory. They cite Dicke's (1957) observation that the red-shift (that is conventionally interpreted as a Doppler shift connected with the speed of receding stars) can be interpreted in a different way: if neutrino density changes with time, the dielectric constant of space changes, and atomic diameters and frequencies change.

Kozyrev's basic assumption is that time is a source of neg-entropy. He claims that "events," causal sequences, set through "time" to modify other events is the vicinity (1968). His language, and his observations, seem easier to understand if we imagine time as being at least partly a a tendency to increase (by consumption of gamma rays and neutrons, and production of hydrogen and neutrinos?), and the ability to act as an "energy source and sink" for a great diversity of physical processes, but with a single directionality or bias.

Thus, Kozyrev's suggestion about time influencing organisms, and his cosmology both overlap with the idea of an ether constituted by

a sea of neutrinos. Another similarity is their rejection of the basic assumption of randomness. It was Einstein's similar desire for a world without a "God who plays dice" that eventually isolated him from most contemporary physicists.

The idea of a sub-quantic medium not only offers a very coherent set of physical explanations, but it provides a very different kind of intellectual world and, more important, it restores objectivity to science, against the neo-Kantian view of orthodox physicists (such as Max Born), and of establishment intellectuals in biology (Monod), linguistics (Chomsky), sociology and anthropology (the structuralists).

The assumption of randomness wherever possible (electrons, nuclear decay, gene mutations, etc.), and the positivistic denial of causality, require a "mathematized" view of reality, which substitutes a very neat and clean knowing for a hopelessly messy and really unknowable material reality. Omitting those very gross assumptions, in favor of a neutrino medium, gives us a material reality which is completely knowable and lawful. Einstein considered the objectivity of reality to be of fundamental importance, but his attempts to achieve a theoretical description of such lawfulness were always within the formalistic tradition, and he considered progress in physical theory to be step by step removing attributes from the "ether."

Neo-Kantianism was flourishing in Germany at the beginning of this century (e.g., Hermann Cohen and Ernst Cassirer). Undoubtedly, this formalistic milieu encouraged the development of physics along similar lines.

By the 1930's, this style of thinking was being explicitly offered as a popular refutation of Marxism. In sociology these ideas have become strong defenses of the status quo: change has been defined as dysfunction. A biologist, Gunther Stent, has recently (1972) tried to give canonical knowledge (narrowmindedness) a biological justification. Many neo-Kantians offer the abstract, non-objective nature of modern physics as support for their view, and the physicists reciprocate by accepting their theory of knowledge in evaluating physical theories.

I view the revolution in physics that is under way as part of a broader cultural liberation.

In biology, it will be a basis for a new beginning.

Many high technologies may result from this new way of thinking. For example, if it turns out that crystals or other states of matter can be

used to coordinate or "pump" neutrinos—and this does seem likely from Dudley's and Anderson's work—it might be possible to achieve nuclear fusion at very low temperatures. (One of the diaproofs of Miller's positive results with his refined Michelson-Morley experimental set-up was a device that used helium gas for the light pathway. This particular "null" result, if Miller's 1000s of experiments are to be accepted as evidence for an ether drift, might have resulted from an ability of helium—a light and symmetrical atom—to resonate with the neutrino sea in a way that would locally adjust the drift to zero velocity.)

Normal science prefers heavy regularities to a tenuous completeness. It is still easy to laugh at the "ether" people, but only if the physicist doesn't read and remember much experimental physics. The "anomalies" are starting to seem more orderly than the "normal" physics.

The ideas mentioned here are intended as a sketch of the possibilities of the neutrino approach—what I want to emphasize is that many things, such as the red shift, that had been treated as answers, should now be seen as problems, still to be solved. If neutrinos offer better possibilities for getting good solutions to any problem, we should proceed to work out all the implications. It is at least certain that nothing can look the same to us once we have considered the possibility of matter and energy interacting with pervasive neutrino fields.

AIDS/Syphilis Treatments & Ideas

Townsend Letter for Doctors, June, 1988

Two of the best articles on AIDS that I have read are by Katie Leishman in *The Atlantic*.[1,2] In the earlier article, she discussed some of the poorly publicized alternative theories about the cause of the disease, and presented some of the arguments about the method of transmission, especially about lice. In the January article, she concentrates on the association between AIDS and syphilis.

Leishman quotes the argument of Jean McKenna, of Berkeley, that the AIDS-associated virus, HIV, is a by-product of the disease, rather than its cause, and that it probably only infects someone who is already immunosuppressed. Reading the older scientific literature, McKenna learned that both Kaposi's sarcoma and pneumocystis carinii pneumonia had been associated with syphilis.

The literature suggested that syphilitic patients are prone to various opportunistic infections, as AIDS patients are, although syphilis does not appear to suppress the immune system until its latent and tertiary stages. She tested twenty-four HIV-positive subjects (most of whom were ARC and AIDS patients) with a documented history of syphilis.

Although all of their FTA (fluorescent treponemal antibody) tests should have been reactive, twenty-one were not. McKenna speculated that all AIDS patients might have syphilis.

In 1981, before AIDS had been recognized, two German physicians, K. Dierig and U. Walthaler, guessed that gonorrheal endocarditis might be causing a patient's hot flashes, drastic weight loss, shortness of breath, and confusion, so they treated him with 40 million units of penicillin intravenously each day for three weeks. His symptoms disappeared, and later they found he tested positive for HIV, and a review of his 1981 laboratory tests "showed abnormalities consistent with AIDS." Dierig and Walthaler then used the same penicillin treatment on six other ARC and AIDS patients. All seven are now "clinically asymptomatic." (The usual treatment for syphilis in the U.S. is a single injection of 2.4 million units of benzathine penicillin. This form of penicillin does not penetrate the brain. In some countries, syphilis is treated for a year.)

Leishman also describes the work of Salvatore Catapano, of Valley Stream, Long Island. Thirty years ago, Catapano learned that the En-

terobacteriaceae stimulate immunity, and found that typhoid vaccine could stop the growth of tumors. When he saw patients with Kaposi's sarcoma, he was reminded of syphilitic sores he had seen in the tropics. Catapano believes that the tropical spirochetal disease, yaws, shouldn't be considered as a distinct disease. He advocates the use of typhoid vaccine to stimulate the immune system before treating AIDS patients with penicillin. Catapano also believes that "syphilis" infections can occur without the presence of a spirochete, possibly by a virus-like variant of the organism. This idea has been proposed many times.[3]

A few months ago, D. J. Bauer of Wellcome Laboratories, wrote an article on the history of antiviral drugs. I know of his 1959 work, in which he showed that copper inhibited the growth of a lipid-coated virus in the brains of mice, so I was surprised to see that he didn't mention copper or zinc, and that his story began with the introduction of amantadine in 1964 to treat influenza (which, like herpes and HIV, is also lipid-coated). I had been interested in amantadine for a long time, because it modifies nerve function in a way (anti-cholinergic) that I think mimics certain steroid hormones which I consider to be part of our natural antiviral defense system. So I was also surprised to see that Bauer gave no explanation of the origin of amantadine.

Amantadine (or adamantaneamine) is a water soluble form (1-amino-adamantane) of a substance that occurs in petroleum. I noticed that adamantane smells like camphor, and that it has a cage-like shape which is very much like that of camphor. Camphor has a long history of use as a germ-killer (e.g., Campho-phenique, for herpes), and was used successfully in the great influenza epidemic 70 years ago. I assume that the idea of using amantadine to treat influenza was based on its obvious similarity to natural camphor. An oxidized form of camphor, camphoric acid, also has a faint odor of camphor, and has been used as an oral germ-killer. It was tested as a syphilis treatment in comparison with penicillin and the traditional arsenic compound, salvarsan, shortly after penicillin became commercially available. All three eliminated the syphilis infection, but the drug companies were already set up to produce large amounts of penicillin profitably. Camphoric acid was used to carry bismuth, another heavy metal that was effective against the syphilis organism. (I was interested in using camphoric acid to transport copper, making it able to enter the brain and also causing it to be absorbed via the lymphatic system, by-passing the liver and thus allowing a large dose

to be absorbed without injuring the liver. I swallowed a small amount, and the next morning, noticing that my mouth felt fresh when I woke up, found that my tongue didn't have its customary coating. I have heard that harmless spirochetes tend to grow on the tongue).

Infection with the "trench mouth" organism, *Treponema Vincenti*, was often associated with a deficiency of white blood cells. Another spirochetal disease, Weil's disease, involved fever, headache, vomiting, and intestinal bleeding. Still another type of spirochetal infection was known in Mexico as "pinta," and mainly involved depigmentation of the skin. Early in the century, some of the abnormalities of pigmentation, teeth and hair development, and defects in blood vessels, that had been attributed to syphilis were found to result from a copper deficiency.

For at least 80 years, people have been observing an association between anesthesia and the elimination of viral infections. We have at least three natural anesthetic systems, namely, the GABA system, the endorphins, and the steroids (especially progesterone). These very likely are just three aspects of a single system. Close analogs of the GABA system are already known to have antiviral action.

About 60 years ago, it was commonly believed that women, especially during pregnancy, are resistant to syphilis. Moore[4] states that it is fair to assume that pregnancy is the factor which suppresses the lesions of the disease. This protection may persist over a long period of years and possibly for a lifetime. Spontaneous cure seems in a few instances to have been the ultimate result.

It seems necessary to believe that some substance produced in the course of pregnancy and non-existent in the tissues and body fluids of males and non-pregnant women is antagonistic to the spirochaetae, but whether this is derived from corpus luteum, or other organ of internal secretion, or from the placenta or foetus, is merely a subject for speculation.[5, p. 684†]

Camphor, progesterone, nutritional supplements, and artificial fever have even fewer side-effects than penicillin, and should be tested more widely. The GABA analogs, besides being non-toxic, have the additional advantage of being very cheap. In the pharmaceutical-bureaucratic world, though, this has too often been a fatal defect.

† Serum copper rises sharply during pregnancy, partly as a result of high progesterone levels. Copper provides some protection against iron toxicity.

The close association between immunity and the balance of iron and copper suggests that the iron/copper ratio should be studied in AIDS.[†] The fact that hemoiderosis (a disease of excess iron absorption) occurs mainly in Africans and in transfusion recipients might be expected to relate to the virulence of any infectious disease in those populations. The tumor of Kaposi's sarcoma is often pigmented with hemosiderin. Although the suppressive effect of iron on the immune system is well-known, it is generally ignored, probably because of our society's obsessive belief that "iron is good for you." Iron's effect on the immune system is interestingly examined by June Goodfield in *An Imagined World*.

Since I mentioned the endorphins above in the context of resistance to infections, I should mention that these endogenous peptides are really a family of substances with very different properties; some activate the right side of the brain, others activate the left side.[6] The two sides of the brain have different effects on the immune system.[7] Opiates are powerful suppressors of immunity.[8] I think it is clear that morphine and codeine should never be used when there is an immune deficiency.

[†] Physicians with AIDS or ARC patients are invited to participate in a study of these and other factors. The Health Discernment Laboratory in Santa Barbara, Calif., will do the serum testing. They will do tests on about 12 of each at no charge, but very special handling of the serum is necessary, and instructions are available.

Abnormal Cells in the Uterine Cervix

Townsend Letter for Doctors, January, 1988

THE membranes of the mouth and of the uterine cervix are very similar, and both are susceptible to development of a supposedly precancerous condition, called leukoplakia. Every winter since I moved to Oregon, I developed areas on the inside of my cheeks where they met my teeth, that became spongy and white, and tended to be imprinted with the shape of my teeth, bulging in a way that caused me to bite my cheek frequently. When I learned that vitamin A would control my dandruff and acne, I then noticed that it also normalized my mouth membranes. A dentist noticed my spongy white spots one winter when I hadn't been taking vitamin A, and gravely warned me that it was a precancerous condition, leukoplakia (sometimes called psoriasis buccalis, or dyskeratosis), and that I should have it checked by a doctor frequently. I went home and took vitamin A, and it was gone within a few days. This experience increased my interest in leukoplakia and led me to read more about it. Because of the similarity of cell type in the cervix and in the mouth, I suggested to a friend that she try vitamin A when her doctor told her that she had cervical leukoplakia, and it cleared up right away.

Since the beginning of the century, it has been known that estrogen is carcinogenic, and by the 1940s it was clear that the hormone of the corpus luteum, progesterone, opposes estrogen's effects, and that it consistently prevented estrogen-induced cancers, and sometimes cured them. In the 1950s, it was learned that vitamin A and estrogen have opposite effects, for example, when applied locally to the skin.[1] It was found that, to a very great extent, progesterone could substitute for vitamin A, meaning that a very large fraction of the vitamin A used by the body is used up in making progesterone, from which the other steroid hormones are made.

Considering these facts, it seemed apparent that optimal treatment of leukoplakia would involve a program to lower the chronic background level of estrogen, while promoting progesterone synthesis. It happens that the body spontaneously moves in that direction, if given the right support. With adequate protein (eggs, milk, cheese, shellfish, liver, etc.), the liver removes estrogen from the blood entirely on its first

passage through the liver, in an otherwise healthy organism. In hypothyroidism, the liver metabolism slows, allowing estrogen to accumulate; also, hypothyroidism appears to allow ovarian cysts to develop and to secrete additional estrogen. While the thyroid hormone promotes the elimination of estrogen, it happens to be essential for the production of progesterone. Vitamin A (with cholesterol) is consumed at a high rate by the corpus luteum, when there is adequate thyroid hormone. However, carotene also tends to be accumulated by the corpora lutea, because of its chemical similarity to vitamin A—it is probably a mixture of vitamin A and carotene that gives the corpus luteum its yellow color—but carotene seems to compete with vitamin A for the active synthetic sites, with the result that too much carotene is toxic to the corpus luteum, and is a fairly common cause of failure to have menstrual cycles. Both vitamin A and carotene, like any unsaturated oil, will tend to inhibit the thyroid, so it is important to balance supplements of vitamin A and thyroid; a sluggish thyroid will more easily be suppressed by large doses of vitamin A, but a high level of thyroid activity causes vitamin A to be used more quickly. It is an interesting expression of this biological relationship that one blood protein carries both vitamin A and thyroid hormone.

To back up this basic process of hormone balancing, there are a few things that can be done besides providing animal protein, vitamin A and thyroid. Vitamin E causes vitamin A to be used more efficiently, and besides taking about 100 units orally, a mixture of vitamin E, vitamin A, and progesterone can be applied directly to the cervical membrane. In rapid cell division, and in estrogen excess, folic acid and other B vitamins are used rapidly, so a supplement might be useful. I have usually suggested a dose of one to ten milligrams of folic acid daily for a few weeks, with liver two or three times a week for the other vitamins. Magnesium is not retained well during stress or in hypothyroidism, so a supplement of several hundred milligrams daily is desirable; epsom salts in orange juice is well assimilated and magnesium oxide should not be used because it is not absorbed. Plenty of bright light helps to maintain progesterone synthesis. Vitamin C and zinc are needed, but will probably be provided by the meat, liver, oysters and orange juice which will provide many of the calories; beans, seeds, sprouts, and seed oils, and raw broccoli or cabbage should be avoided, because they can disrupt the hormone balance.

I personally had contact with 35 women who were advised to have a hysterectomy because of abnormal cells found in Pap smears or biopsies, but who wanted to try this approach for a month or two. All of those women had normal tests when they went back to the doctor, usually in two months. Later, I heard that groups had been formed to teach the method, but I haven't heard whether the results continue to be 100%.

Age Pigment

Cause and Effect of Aging and Stress

Healing Village E-Zine, December, 2013

I have written about the many toxic effects of unsaturated oils, estrogen, and excess iron, and how each of these contributes to certain features of aging and age-related degenerative diseases. Now I am going to discuss some of the ways those toxic effects converge, creating a new, "terminal toxin," and how some of the features of aging can result from the presence of this toxin. Rather than using the vague idea of "free radical damage," I think I can show a simple mechanism by which the terminal toxin, lipofuscin, produces the essential features of aging. I suspect that familiarity with this mechanism will be a necessary step in understanding how the high-energy cellular state of youth can be restored.

The word, "lipofuscin," is coming into common usage, so it is worth knowing that its root meaning is "dark fat." The root, fuscus, occurs in the word obfuscate, to obscure. Biologists, who know about the dye called fuchsin, which has nothing to do with lipofuscin, often confuse the words and mispronounce lipofuscin.

In pointing out how oils, estrogens, and iron contribute to aging, I don't mean to distract from their specific toxic effects; rather, those specific effects become more harmful as the organism is weakened by aging.

Lipofuscin, ceroid pigment, age pigment, and liver spots all describe approximately the same thing, though each researcher tends to insist on certain idiosyncratic distinctions, because there is still hardly a "scientific culture" of averaged-out terms and concepts. This is a strange situation, since the substance has been studied occasionally since the first report in 1842, making it scientifically about as old as organic chemistry itself. In 1954, I asked my biology professor (who was in his sixties) what he thought the cause of aging was, and he said some people believed that it was the result of the accumulation in cells of insoluble metabolic by-products, called "metaplasm." His remark was in my mind later when I watched an amoeba dividing under the microscope; it seemed to have become sludgy, viscous, and lethargic, and then as it divided, the new

cells appeared to be moister and more elastic, as if they had diluted some kind of ballast that produced internal friction.

In 1954 there was a report of a girl whose skin turned black from using an ointment containing estrogen. Later, in the 1960s, I noticed that many women using birth control pills developed patchy brown spots on their faces. As I read more about pigmentation, I saw that estrogen, like a variety of irritants, promoted the development of ordinary dark pigment, melanin, in the skin, and that this was different from the liver spots or age pigment that often begin to appear in middle age, and that become so noticeable on the hands, arms, and faces of most old people. As it turns out, both types of pigment are produced by oxidation of smaller molecules which causes them to coalesce into complex masses, but at that point the difference becomes total. Melanin protects against further oxidative injury, but lipofuscin tends to promote further injury. Later, I learned that estrogen was implicated in the production of age pigment, at least in the uterus.[1,2]

Another kind of pigmentation, that is sometimes seen in the skin around the eyes, has been found to contain substances derived from hemoglobin. The heme/porphyrin pigments are interesting in relation to aging, not just because estrogen is known to be involved in the overproduction of the porphyrins, but because lipofuscin has been reported[3,4] to contain the heme group, and because the metabolites of heme (the bile pigments;[5] pyrroles[6]) have been associated with cancer. (As I have mentioned elsewhere, the metabolism of heme produces carbon monoxide, which could produce a self-sustaining respiratory defect.)

That estrogen should have a role in three different types of pigmentation is interesting. What common feature is there in the physiology of these pigments that relates to estrogen?

(Some sources describe a syndrome—Sprinz-Nelson/Dubin-Johnson syndrome, or maverohepatic icterus—that supposedly involves the accumulation of all three pigments—melanin, porphyrin, and lipofuscin—in the liver. The simultaneous formation of different types of pigment might account for some of the disagreements in the study of lipofuscin.)

Melanin is produced in the skin under the influence of ultraviolet light, and in the brain's substantia nigra, it is believed to be produced in relation to a free-radical-generating cycle of dopamine metabolism. Since melanin is an effective antioxidant, it is assumed that its formation represents a defense against free radicals. In the skin, ultraviolet light's

primary "target" appears to be the polyunsaturated fats, in which it produces free radicals. Estrogen—especially when it has been changed into the catecholestrogen form—is known to participate in futile cycles of oxidation-reduction, with the production of free radicals. In 1972, I demonstrated that estrogen powerfully promoted the reduction of the dye, TTC, possibly by such a free-radical mechanism.

Lipofuscin is produced by the over-feeding of unsaturated fats (such as fish oils[7]) and the underfeeding of vitamin E, relative to the amount of unsaturated oils.[8] Ultraviolet light, iron, and aluminum promote its formation, apparently by the production of free radicals. The free radicals generated by estrogen, and by estrogen's promotion of iron absorption, would contribute to the lipid peroxidation. Stress, which is known to intensify free radical production, also accelerates the production of lipofuscin.[9] I have found that estrogen[10] induces cellular conditions that resemble those produced by x-rays and carcinogens,[11] and which probably reflect the production of superoxide or other radicals.

Porphyrins are known to be produced under the influence of estrogen, but anything which interferes with cellular respiration appears to stimulate their production, as part of a mechanism of adaptation to oxygen deficiency that leads to the production of more hemoglobin. Lipofuscin itself contains the heme group, and wastes oxygen in a sort of short-circuit between NADH and oxygen (NADH-oxidase[3,12]). This is also one of estrogen's important effects.

While the formation of melanin seems to be one of the healthy responses to free radicals, and is governed by an enzyme system, lipofuscin seems to be produced nonenzymically, directly by the damaging free radical process itself, and the porphyrins are apparently an adaptive response to oxygen deprivation, rather than to an excess of free radicals.

There would seem to be a sequence of events. If the antioxidant defenses, including melanin formation, are inadequate, then lipofuscin would be formed. If the consumption of oxygen by lipofuscin is sufficient, the heme-synthetic pathway would be activated.

One of the reasons for the lack of interest in lipofuscin has been the doctrine that it is nothing but a little harmless "extra baggage" the cells have to carry, that couldn't account for all of the changes that occur in aging. "Somatic mutations" have been offered as an explanation for the age-related increase of cancer, atherosclerosis, diabetes, arthritis, autoimmunity, and even for the metabolic slowing that is characteristic

of aging. The basic doctrine of aging, held by those in power, has been that, since it involves a generalized slowing of most biological processes and loss of precise regulation, and since the "genes" are held to control all cell processes, the essential changes must happen in the nucleus. Lipofuscin occurs in the cytoplasm, and sometimes is found outside of cells, so its role "must be passive," according to that mainline doctrine.

But exactly the opposite view—that the crucial changes that accompany aging occur in the cytoplasm—fits the evidence more accurately.

For example, there is a steady dehydration of tissues with aging, and a slowing of metabolism. The ability to tolerate stress decreases with age, and chromosomes seem to be easier to damage, and slower to be repaired. According to S. J. Webb, the cell's "bound water" protects against radiation-induced mutations. Since DNA repair is a process that consumes energy, the lower metabolism and low energy production which result from dehydration could lead to an accumulation of mutations. But no one has ever proposed that mutations cause the steady dehydration that occurs with aging. (The dehydration, I think, is most likely a defensive reaction of cells, maybe involving the heat-shock/stress proteins, to preserve the cells' domain of control over their metabolic water, under conditions of limited energy production. I think this resistance against the uptake of water helps to maintain the differentiated state, and to prevent uncontrolled growth.)

If the cell's ability to retain water is partly dependent on ATP, as Gilbert Ling has shown, then interference with energy production could cause the dehydration, in a vicious circle. If lipofuscin interferes with the cell's energy production, or ability to retain water, then it is in a position to create some of the characteristic features of aging. In S. J. Webb's studies of bound water, he found that inositol protected cells by helping them to retain water. His studies are especially interesting, considering Lehninger's observation that "mannitol, or other polyhydroxylic solutes" cause mitochondrial swelling, or inhibit their contraction. (Mannitol is a straight-chain analog of inositol.[13, p. 188–191]) Thyroxin also causes mitochondrial swelling.

In Ling's view, ATP causes cells to retain water in a tightly organized form, and when ATP is seriously depleted, adsorbed potassium is released to become osmotically active, and sodium and chloride enter along with water, which is then in the "loosely held" state of normal bulk water, lacking the special properties of water that had been dominated

by polymer surfaces. This swelling has been called "depolarization swelling," and is partly responsible for the swelling of injured or dying cells. Presumably, less drastic energy changes will cause physiological changes in the amount of organized water, in which water is usefully retained in proportion to the energy level.

While rodents live a year or two—and die in a much more hydrated state than people or animals that live approximately a century—at the end of a rodent's normal life span its cells (e.g., brain and heart) contain as much lipofuscin as the cells of century-old people do. Dogs accumulate lipofuscin about 5.5 times as fast as people do, and people live about 5.5 times as long as dogs. This is just what we might expect if lipofuscin is the "terminal toxin." Loss of cell water would have an influence, but wouldn't be the decisive factor. (The total amount of water in a cell doesn't matter so much, if the energy-producing and functional parts of the cell are deenergized and dehydrated, impairing the cell's responsiveness and adaptability.)

Besides energy production, probably the cell's most basic mechanism of adaptation is the alteration of its structure, which is going on constantly, with the production of new proteins and the destruction of old proteins. This "protein turnover" slows with aging, and the change is mainly on the side of decreased ability to break down old proteins. Lipofuscin directly inhibits the proteolytic enzymes which break down proteins. Unsaturated fats have a similar action, even when they aren't noticeably converted into lipofuscin. They inhibit mitochondrial energy production, which obviously could affect synthetic processes, but it has been known for many years that they also inhibit proteolytic enzymes, although this information tends to be familiar only within certain contexts, such as food chemistry, clot chemistry, immunology, thyroidology, etc.

The mitochondria are continually being repaired and replaced. Inhibition of proteolytic enzymes will cause their repair and replacement to lag, with the result that these crucial energy-producing organelles will "age."

There is evidence indicating that lipofuscin forms in lysosomes and as degenerate mitochondria. With a mitochondrial origin, heme would be present because there are heme-containing enzymes in the mitochondria, but any lipofuscin forming primarily within lysosomes could also absorb heme-like groups from other sources.

It is the heme group which gives the lipofuscin particle the NADH-oxidase function, described by Bjorkerud. Measured in a respirometer, lipofuscin granules respire similarly to mitochondria, except that they do not produce any ATP. As a result, a large amount of lipofuscin will compete with mitochondria for the oxygen which is available to the cell, and will also consume the energy that is available as NADH, and will lower the cell's ability to produce ATP and to function.

When mitochondria are activated, they swell. The swelling-contraction cycle of normal activity is relatively slight. Another kind of swelling, associated with lipid peroxidation, is more extreme, and leads to the destruction of the mitochondria. (Iron, excess unsaturated fats, and many other substances that react with sulfhydryl groups—incuding glutathione—can cause this kind of swelling.) For every molecule of oxygen consumed by cytochrome oxidase, two molecules of water are produced. If lipofuscin is consuming the oxygen, it will produce the water, and the underfunctioning mitochondrion will produce neither ATP nor water, as a consequence of inadequate oxygen. Lipofuscin, therefore, will tend to dehydrate the mitochondria. Anything that inhibits respiration seems to inhibit the physiological swelling. Besides the small contribution of metabolic water, there are probably physical processes associated with respiration that govern mitochondrial water content.

Mitochondrial activation is associated with swelling, and extreme mitochondrial dehydration very likely represents a failure to produce energy effectively, and I suspect tends to cause the destructive collapse of the organelle. But elsewhere in the cell, the vicinity of the lipofuscin will tend to become hydrated, and this wouldn't be subject to the regulating effect of ATP.

Estrogen's early effects include activation of dehydrogenases and peroxidase,[14–16] and it participates in the interaction of NADH and NADPH as well as in the oxidation of NADH.[17–21] The oxidation of NADH is involved in many harmful free radical processes.[22] The most visible early effect of estrogen is to stimulate water-uptake by the cell. How it causes this immediate swelling isn't known, but it probably involves this consumption of oxygen, since simply cutting off the cell's supply of oxygen also causes water-uptake and edema. (Maybe ATP is needed to "extrude" water from the cell generally, as it is in the mitochondria.) The oxidation of NADH tends to raise the pH of the cell, and

by increasing the electrical charge of the proteins this would be likely to cause swelling. I suspect that the normal (respiratory) function of oxygen is to adjust the electrical charge of the cell proteins, in a way that favors ATP synthesis and controls hydration. ATP (which is an acid, and is strongly adsorbed to proteins, influencing their charge) is known to cause swollen mitochondria to extrude water.

Although the exact meaning of the NADH-oxidase NADH-peroxidase activities isn't known, it is interesting that they are so strongly affected both by estrogen and by lipofuscin. Whatever else these enzyme-functions do, they waste oxygen and consume the cell's energy, producing free radicals in the process.

Unsaturated fatty acids have a higher affinity for water than saturated fats do. In the presence of water, they swell. To isolate functional mitochondria, it was discovered that hypertonic sucrose stabilized the mitochondria, apparently by opposing a strong tendency to swell. But when animals are fed a diet rich in unsaturated fats, the mitochondria have a lower swelling tendency than do those of animals that are "deficient" in polyunsaturated fats. This is the opposite of what might be expected from the physical behavior of the unsaturated fats, so the difference probably involves the metabolic activity of the mitochondria, rather than their physical chemistry. ("…the active swelling stimulated by respiration has a high temperature coefficient, which is consistent with a chemical or enzymatic process…"[13, p. 184–185]) For one thing, the unsaturated fats simply block respiration by blocking the electron transport chain, and by inhibiting cytochrome oxidase. In fetuses and young animals up to the time of weaning, one site of the cardiolipin molecule, which is essential for cytochrome oxidase function, contains the saturated fat, palmitic acid. After that, as the animal's respiratory activity declines, the palmitic acid is replaced by linoleic acid. At the same time that respiration is being inhibited by the unsaturated fats, lipofuscin begins to accumulate, further interfering with respiration, by consuming oxygen outside the mitochondria.

When fed a diet high in unsaturated fat and low in vitamin E, lipofuscin forms rapidly, and the incidence of cancer and other diseases of aging—including diabetes—increases greatly. (Regarding glucose metabolism, Barnard, et al.[23]; many more references are given in my article on diabetes, scleroderma, and oils.)

It is interesting that the first publication identifying dietary fat as an essential cause of cancer (1927) appeared almost at the same time as the demonstration[24] that a substance resembling lipofuscin could be produced by bubbling oxygen through unsaturated fat (fish oil). Various types of unsaturated fish or seed oils have since then been used to produce lipofuscin *in vivo* and *in vitro*.

Hartroft and Porta[8] demonstrated that the pro-oxidant metals, especially iron, accelerate the formation of age pigment, and recent experiments confirm those observations.[25] Aluminum and silicon, which have a role in brain and blood vessel aging, also have a role in the formation of age pigment.[26]

My observations of extracts of aged tissue, soaked in ether or pyridine, showed an absorption spectrum in the ultraviolet frequencies that indicated the pigment was a complex mixture with unsaturated fats, but with the specific absorption indicating the presence of heme or related material.

When artificial lipofuscin, made by ultraviolet irradiation of mitochondrial preparations, is added to cell cultures, the cells act as if they had aged suddenly, and then die.[27]

Similarly, when mitochondria are extracted from old cells, and injected into young cells, the young cells behave as if they had aged.

One of the remarkable things about the NADH-oxidase described by Bjorkerud is that it is cold-inactivated. I have argued[10,28] that estrogen activates enzymes of this type, but a mere excess of water could have a similar function, and if these granules produce their own water, they will tend to support the condition which activates themselves, while also tending to decrease the metabolic activity of mitochondria. Where the water is being produced, there is a lack of ATP, and where the ATP is being produced, there is a limiting lack of oxygen. While estrogen causes cells to take up water immediately, before any other cellular change is seen, my argument has been that it makes the cellular water more "bulk-phase" like, with less of the structure (vicinal water) evident in water near surfaces; this argument is based on NMR studies of water in tissue treated with estrogen.[10] The damaging effects of estrogen on mitochondria,[29] in this view, might be the result of changing enzyme activities by affecting water structure, as well as of causing a redistribution of water between cellular organelles.

Estrogen causes changes in collagen synthesis that resemble changes occurring in aging[30,31] and in oxygen deprivation.[32] The theory that cross-linking (hardening) of collagen causes aging is popular,[33] but it seems odd that the idea of interactive factors in hypoxia—estrogen, collagen, and lipofuscin—hasn't been of greater interest. Hypoxia,[34] radiation, and stress (lipofuscin accumulation with restraint stress[35]) like estrogen, cause accumulation of collagen and lipofuscin, and lipofuscin contributes to hypoxia and stress. The fact that puberty in girls is accelerated by unsaturated fats, and delayed by their deficiency, is just one of the many indications of the close connection between estrogen and the unsaturated fatty acids.

The doctrine that radiation causes cancer simply by causing mutations has grown up in the scientific culture that has paid essentially no attention to lipofuscin. All sorts of ionizing radiation produce free radicals in unsaturated oils, and so naturally radiation will contribute to the formation of the age pigment. In the depleted, low energy state that develops when a large amount of lipofuscin has accumulated, chromosome damage will occur, and will not be repaired as it is in the youthful high energy state. Mutations in themselves don't cause aging,[33,36†] but aging creates a disposition for mutations to accumulate. (It was found that men who exercised before breakfast produced large numbers of chromosome breaks. The energy provided by breakfast made a visible difference in the amount of chromosome damage produced by exercise. The chronic low energy state that results from being full of rancid fat must amplify the damage done by ordinary stress.)

Minimizing radiation, of course, is important, and if we aren't primarily worried about radiation as a direct mutagen, the comforting thought of a "threshold of safety" disappears. The same principle applies to the avoidance of environmental toxins (so many of which are estrogenic), since the factors that promote age pigment all seem to be additive. The age pigment is a final common pathway in which many types of damage converge, in the way many different factors converge in the drying of paint. By depleting the cell's energy, lipofuscin accumulation causes trivial challenges to become increasingly harmful, in a vicious circle that tends to accelerate the production of lipofuscin.

† See quotation at the end.

Some of the factors that significantly accelerate the formation of lipofuscin—dietary polyunsaturated fats, deficiency of vitamin E and selenium, and excess iron—are things that can be manipulated without great effort. Some of the proven factors that retard its formation, such as a low calorie diet, are not so easy to sustain, and require some study.

If a "program in the genes" controlled the rate of aging, dietary modification should make no difference at all, but calorie restriction slows the rate of aging, as it slows the rate of lipofuscin formation.[37,38]

The doctrine of "programmed aging," and the Hayflick doctrine, maintain that cells have an innate capacity to undergo about 50 divisions, and that "aging" consists of having used up their limited capacity for division. It is clear that the medium in which the cells are cultured affects their ability to multiply, and that serum from old animals slows their growth. The experimental data from human cells cited by Hayflick oddly fail to support his theory. For example, cells from a sick 87-year-old person underwent 29 divisions in culture, and those from a 26-year-old person killed in a car accident were able to divide only 20 times in culture. Cells from a single individual, in different (repeated) cultures show very different "limits."[39] The appropriateness of the culture medium for the particular needs of the cells seems to be the issue, and all cells do have a "memory" or "program," reflecting their developmental state and function. Because of this cellular memory or inertia, a damaged condition might be passed on to daughter cells, and even to a subsequent generation or two, before full vigor can be restored. Historically, these "lingering effects" of the environment have been called "dauer-modifikationen." I believe our present level of pollution, by this sort of lingering effect on development, is going to produce an increasing incidence of birth defects, immunodeficiency, accelerated aging, and cancer, if biological remedies aren't found to neutralize its effects. The harmful effects of estrogen—DES, for example—persist for generations. Besides the hundreds of estrogenic chemicals accumulating in the environment, medical estrogen has been prescribed for approximately 200 stupid purposes. Harvard Medical School lent its prestige to the deadliest and most anti-scientific of these promotions, and government agencies have endorsed the fools and colluded with the criminals. Similar medical/industrial/governmental conspiracies have operated in many other areas, notably in the use of iron and seed oils.

The Possibility of Remedies

There is evidence that cells can clear themselves of lipofuscin, but the mechanism isn't understood. As a result of low oxygen tension in the fetus, lipofuscin appears, but then disappears after birth. The composition of this material could be different from the material that develops later, but the greater metabolic activity of the newborn is probably related to the ability of cells to destroy it or to excrete it. Recently, it has been proposed that a variety of psychotropic drugs promote its excretion,[40] but most of those drugs have serious side effects. In cultured brain cells, it was found that vitamin E and ethyl alcohol promote its disappearance. Since alcohol's toxic effects largely derive from its interactions with unsaturated oils and iron, a small amound of alcohol might be useful in clearing lipofuscin. I have often seen topically applied vitamin E with progesterone remove age spots from the skin. In younger (age 45 to 55) women who have developed the spots while using estrogen, the spots sometimes disappear when they stop using estrogen. In much older people, the use of vitamin E and progesterone has sometimes only caused the spots to slowly become lighter, during several months.

Since lipofuscin contains proteins and metals as well as fats, it has been suggested that activation of proteolytic enzymes would facilitate its removal, but it is partly the inhibition of proteolytic enzymes by lipofuscin that makes it a difficult problem. The low calorie diet which delays the formation of lipofuscin is known to increase the activity of proteolytic enzymes, and I think this is largely the result of reduced exposure to unsaturated fats. According to the Shutes' research, vitamin E facilitates the clearing of blood clots by activating proteolytic enzymes. At the time they were doing their research, it was recognized that estrogen and unsaturated fats inhibit proteolytic enzymes. While the heart-disease industry has done a lot of pharmaceutical research on the regulation of the clotting process, there is much less research on the proteolytic enzymes which remove clots. The Shutes introduced the issue more than 50 years ago, and I suspect that their observations showing that vitamin E, thyroid, and progesterone protect against heart disease by opposing the clotting effects of estrogen (and unsaturated fats) came too close to saying that the problem can be solved without the help of the great drug industry. A solution for degenerative diseases which shows

estrogen and polyunsaturated oils to be essential parts of the problem is not one that will find many research grants.

To me, the chemistry of lipofuscin indicates that we should minimize our exposure to unsaturated fats, iron and other metals, and estrogen, while cautiously exploring the ways to prevent their cumulative damage. Since many things promote oxidation in one context and inhibit it in another, caution is important in exploratory research. Copper, for example, can cause harmful oxidation, but it is required for melanin synthesis, superoxide dismutase, cytochrome oxidase, and other enzymes, and its deficiency leads to intense oxidative damage from iron. When there is clear evidence that a particular form of copper is safely assimilated, it might be a desirable food supplement. At present, I think mollusks and crustaceans are the safest sources of copper.

Many "antioxidants" that are being promoted for medical/nutritional use are seriously toxic, even mutagenic or carcinogenic. The "adaptogen," mildronate, protects mitochondrial ATP production by restricting the oxidation of long-chain fatty acids. This type of antioxidant seems to reinforce natural protective processes,[41] and is not likely to have the toxicity of the phenolic, or polyphenolic, antioxidants. Other particular therapies for aging might include direct restoration of ATP and hypoxic (high altitude) adaptation to stimulate the regeneration of mitochondria.

Currently, I think the most important issue is to find foods that are practically free of the polyunsaturated fats. Low fat milk and cheese are suitable, and are desirable because of their low iron content, but are not ideal for an exclusive diet. A supplement of vitamin E and coconut oil should have a significant effect on the rate of aging : the effect of coconut oil is to reduce the need for vitamin E, to act as a dilutional chain-breaker in free radical propagatioin, and to provide energy at a high level to repair cell damage. While unsaturated oils contribute to the inlammatory process (and there is serious question as to why evolution would produce the mechanism of inflammation, since its effects on balance seem harmful), coconut oil doesn't, and the inflammatory "eicosanoids" made from the "essential" fatty acids probably contribute to the formation of age pigment in certain situations, such as in atherosclerosis. Since free radicals are produced in the formation of prostaglandins, aspirin and other antiinflammatory drugs have a sort of antioxidant effect, which might explain their apparent role in the prevention of Alzheimer's disease.

The thyroid hormone itself has been found to be protective against lipid peroxidation, and even against radiation damage, and thyroid function is promoted by coconut oil. Proper thyroid function minimizes the production of adrenaline, and adrenaline—like estrogen—increases our exposure to fatty acids. Potatoes and many fruits are fairly low in the unsaturated fats and iron. The ketoacid equivalents of the essential amino acids are found in some plant materials that are very low in unsaturated fats and iron. When the right combination can be found, it would be possible to have varied foods that provided calories, minerals and vitamins, with either protein or a protein equivalent, which wouldn't lead to the accumulation of unmetabolizable fats and metals.

An important, but neglected, aspect of respiration, resulting from proper thyroid function, is the production of carbon dioxide. Carbon dioxide has some remarkable properties, including the regulation of circulation and mineral balance. I believe it probably has a direct role in the production of ATP, and by its physical-chemical effects, it might be an essential factor for activating the enzymes of the lysosomes, which have the capacity to clear age pigment from cells. The effects of diet, hormones, and oxygen deprivation on aging and lipofuscin could be mediated importantly by their effects on the production of carbon dioxide.

An outstanding feature of the "false respiration" of lipofuscin is that it produces no carbon dioxide.

Aging Ovaries: Not the Eggs

Townsend Letter for Doctors, August/September, 1995

A few months ago public television ran a long program on the menopause, in which a rather glamorous woman physician said some shockingly ignorant things about the ovaries and menopause. I went to some book shops, to see what she might have been reading, or hearing in conversation.

One writer thought it would be nice to change the name of the menopause to "the pause." Another said it is too judgmental to say that the ovaries "fail" at menopause, and that they are really just maturing. Those concerns with terminological politeness remind me of Woody Allen's remark about death—that it is nature's way of telling us to slow down.

All of these current paperback books about menopause subscribe to the same doctrine about reproductive aging. Uniformity of opinion creates an environment in which publishers who want to sell a lot of books feel that they have to publish things that don't disturb the reading public. Books about menopause become books about an attitude toward menopause.

Even people who like to say that ovaries "don't fail" at menopause describe a theory in which menopause and its consequences are the result of the disappearance of eggs from the ovary. That theory is so simple it can be described in three short sentences, none of which is true: (1) ovary runs out of eggs; (2) ovulation produces hormones, so you can tell when ovulation stops because the ovaries stop producing hormones; (3) menstruation stops because ovulation has stopped. Those principles are surrounded by various corollaries. "Estrogen is the female hormone." "Estrogen deficiency accelerates aging." "Treatment with estrogen makes you more feminine." "Progesterone deficiency is the result of anovulatory cycles."

Many experimenters have demonstrated that old animals that have become infertile keep producing eggs. Several experimenters[1] have removed eggs from the ovaries of old animals, and transplanted the fertilized eggs into young animals, where the embryos were able to implant and develop normally.

I found that old animals had too little oxygen in their uterus to keep the embryo alive at the time it would normally be ready to implant itself in the uterus. Giving estrogen to a young animal causes a similar lack of oxygen in the uterus, and prevents implantation of the embryo.

At the time old animals would normally have become infertile, they remain fertile if they are given a supplement of vitamin E and progesterone.

It is now established that aging animals, at the time they become infertile, are deficient in progesterone, but still produce estrogen. Even in young individuals, when stress occurs around the time of ovulation, interference with progesterone production will prevent implantation. If progesterone becomes deficient after the embryo has become implanted, miscarriage occurs.

Estrogen, acting alone or with insufficient progesterone, causes spasms in the spiral arteries that provide oxygen and nutrients to the endometrium. This seems to be the basis for menstruation, and is also believed to be a factor in miscarriage.

About 30 years ago, researchers began to understand that reproductive aging was not caused by the lack of eggs, and the aged uterus was able to support pregnancy if it had the right hormonal support. Interest turned to the brain cells in the hypothalamus which regulate the pituitary. G. H. Zeilmaker[2] was one of the first to suggest that ovarian hormones caused the brain to age. More recently, P. M. Wise[3,4] has clearly demonstrated that estrogen exhausts the cells which inhibit the pituitary gonadotropins, with the result that even abnormally high levels of estrogen are unable to turn off the pituitary secretion of the hormones that drive the ovary. Estrogen itself can impair the ovary's ability to produce progesterone, but the continuously high secretion of gonadotropins disturbs the ovary, the adrenals, and (according to recent observations) even the uterus.

Stress, especially when augmented by estrogen, leads to injury, exhaustion, and aging. The uterus and ovaries participate in the response to stress, but (as Zeilmaker and Wise have shown) the brain proves to be more directly involved in menopause than the ovaries or uterus. Coordination turns out to be crucial for complex processes such as ovulation, fertilization, and implantation. The destruction of the nerve cells that regulate the pituitary makes coordination impossible.

The issue of "running out of eggs" can be settled simply by demonstrating the presence of viable eggs at the time reproductive ability has ended. In the 1940s, menopause was "explained" in terms of an estrogen deficiency, without a basis in fact, and now an "egg deficiency" is combined with the "estrogen deficiency," compounding the confusion. Facts aren't everything in science;[†] it is necessary to look at the context from which these ideas develop.

Two of America's most productive researchers in reproductive physiology, Edgar Allen and Herbert M. Evans, made observations that they believed showed that the germinal epithelium of the ovary goes through a cycle of cell proliferation that produces a new generation of oocytes during each menstrual cycle. It is recognized that new egg cells appear in the ovaries of adult prosimian primates, and at puberty in cats and pigs. Observations of newly developed egg cells have been reported in some other species. But the dominant view prefers to see the number of egg cells declining from birth, or earlier, with absolutely no new egg cells being formed later.

During gestation and infancy, the gonadotropins are very high. These hormones decline during childhood, during the time that the number of egg cells is so visibly declining. The high level of the gonadotropins during infancy hasn't been explained, but it is reasonable to suppose that it has something to do with the development of the ovaries, since a "developmental" function can be demonstrated for the gonadotropins in the ovaries and testes of older animals.

The number of brain cells peaks a few months before birth, just as the number of egg cells does. Many people have argued that this somehow means that brain cells are incapable of dividing after infancy, though there is no factual basis for making that argument, and in fact

[†] Since the 1930s, estrogen's toxic potential has become very clear. However, the estrogen industry doesn't want people to understand that estrogen is a shock hormone with pro-aging effects. Histamine mimics estrogen's effects on the uterus, and antihistamines block estrogen's effects.[5,6] Estrogen mimics the shock reaction. Stress, exercise, and toxins cause a rapid increase in estrogen. Males often have as much estrogen as females, especially when they are tired or sick. Estrogen increases the brain's susceptibility to epileptic seizures, and recent research shows that it (and cortisol) promote the effects of the "excitotoxins," which are increasingly implicated in degenerative brain diseases.

adult brain cells are now known to be able to divide. (That is true of heart cells, too.)

In a variety of tissues, it can be shown that the presence of mature cells inhibits the division of other cells. If part of the liver is removed, the remaining cells divide to replace the lost tissue. If the skin is cut, cells divide to help fill in the defect. If there is an adequate number of egg cells, this principle suggests that there is no need to produce more. There is a treatment for polycystic ovaries called "wedge resection." This can reduce the production of masculinizing hormones. By analogy with other tissues, it seems likely that the removal of a mass of malfunctioning tissue leads to the growth and development of new cells which function the way a new ovary would. Regeneration seems to be a capacity of every tissue, given the right environment. If the ovary were studied after such treatment, I suspect that "new eggs" would be found. (But even in the seemingly simple process of healing a wound in the skin, there is still disagreement as to the relative contribution made by local cell division, and the invasion of the region by structural cells from elsewhere in the body. The appearance of a cell can be misleading; histology is often a matter of making educated guesses. For example, white blood cells can look like epithelial cells.)

Although the question of whether all the woman's eggs are in existence at or before birth doesn't logically have anything to do with the other question, whether there are still eggs in the ovary at menopause, there is a reason that people connect them. This has to do with the idea of a "germ line" as distinct from the "somatic cells." The eggs are "from the germ line," all the rest of the body (and much of the ovary) is a different sort of stuff. The "germ line" has the special property of immortality and it is "isolated" and independent.

The body is susceptible to being modified by the environment, and is mortal. These are the traditional formulations of the idea, and the people who learn their orientation from textbooks are not necessarily conscious of how the ideas fit together. For biologists of my professors' generation, these ideas seemed to be a sacred core of biology, but with their death, maybe biology can be liberated.

August Weismann, working at the end of the last century and the beginning of the 20th century, created the basic ideology of genetics, to combat the idea of the inheritance of acquired characteristics, which had been supported by Darwin and others. He argued that the hereditary

substance, or germ plasm, was derived only from preexisting germ plasm, and couldn't be formed anew, or modified by the environment. It created every part of the perishable body, by a process in which traits were segregated, so that the germ plasm contained the full complement of hereditary material, and each part of the body contained only the limited fraction needed for its characteristics. Thus, the body was inferior created material, while the germ line was the immortal creative stuff. Since the body adapts in response to the environment, it had seemed that these changes would be passed on to descendants, until Weismann's argument showed that it was only the perishable, dead-end body lacking the hereditary principle which was adapting. The germ line was somehow isolated from the body and from the environment.

Weismann's theoretical germ line became identified with the chromosomes and the genes. His theory was shown to be simply wrong, in that each type of cell in the body contains a full complement of chromosomes and genetic information. Although his facts were wrong, his ideology became deeply embedded in the culture of genetics. To keep the idea that the "germ line" is somehow something distinct from the body required a special effort, once the chromosomes were seen to be identical in every part of the body. Weismann's whole point in his "germ line" idea was to show an absolute distinction between the body and the hereditary substance. If his ideology that had been built to deny the inheritance of acquired characteristics were to be saved, the isolated germ line would have to be found elsewhere than in the chromosomes.

The idea of "germ line (or *Keimbahn*) determinants" now took over, and was believed to be something in a certain spot in the egg. As the egg divided, into cells that look very much like each other, the cells which came from that part of the egg represented the germ line. As the embryo developed, the region that seemed to be traceable back to that part of the egg, represented the germ line. As the gonad began to grow, cells from the region representing the germ line were thought to travel over and invade the gonad, where they multiplied into vast numbers, but always remained the same isolated strain of germ cells with their "separate" history that could be traced back to the determinants in the special place in the egg. During the early days of embryonic development, these immigrant cells looked exactly like their neighbors which were somatic cell sprouts from the embryonic kidney region.

If it weren't for the ideology of absolute isolation of the hereditary substance, an embryologist might have suggested that cells or material of one part of the embryo induced a specialized, differentiated state in some cells that happened to be suitably located. If the cells derived from that certain part of the egg didn't carry unique genetic material—and they didn't—then what they carried with them was an incipient state of differentiation. Why the big deal about that particular history of differentiation? It was because the ideology that motivated Weismann was still active, and its purpose was to argue that only the "gene" was the creative productive source, and that the body—the "somatic cells"—was the passive product, whose adaptations meant nothing in the long run. This has been called the "central dogma" of genetics, that information flows only from the gene to the cell, and not back from the cell to the gene. That ideology forced geneticists to deny the existence of RNA viruses (including retroviruses such as the HIV-"AIDS" virus), and is still active in blocking research on the prion or scrapie virus, which is a protein. To say it bluntly, many highly respected biologists acted stupidly because they blindly believed in a false ideology.

Incidentally, this ideology was always impossible for horticulturists to accept, since they were in the habit of grafting (cloning) vegetative (somatic) parts of plants, which would then produce flowers and fruits. For them, the "germ" was often a product of the "body." Luther Burbank's work was consistently ridiculed by the academic biologists, who believed his achievements were impossible, that is, fraudulent. Many of Burbank's perceptions have been supported by recent evidence, but they couldn't be accepted by people whose ideology of the germ line/somatic distinction seemed to be contradicted by his work.

Another problem with the doctrine of the germ line was revealed when embryologists separated the embryo at a very early stage into two groups of cells, and found that each was able to grow into a complete animal. The idea of the germ line predicts that one member of the pair of twins could get the ability to reproduce while the other would be sterile. Some important ideas can survive their disproof.

It is exactly the same academic ideology of the priority of the germ line which blames the whole complex process of reproductive aging on the mechanical process of an "ovary running out of eggs." The ovary doesn't run out of eggs, and running out of eggs would have no great consequences if it did happen, because the main events in ovulation are

produced by cells other than the eggs. But the ideology says that the "germ line" controls everything, and the eggs are the germ line. In other words, genes control the organism, and eggs control the woman.

I think it will be instructive to consider the three steroid secreting glands—ovaries, testes, and adrenals—together, to see what they might have in common. In the testes, it is generally believed that pituitary gonadotropins regulate steroid synthesis and gametogenesis. In the ovaries, the gonadotropins also regulate the production of steroids, and—to some extent—the production of eggs, if not the whole gametogenic process. In the adrenal, ACTH governs the production of cortisol and sex steroids, and the transformation of the glomerulosa cell type into the other types, which secrete those hormones.

The outer layer of cells in the adrenals can form the other two cell types, and since stress ACTH converts them to the other types, new ones must be formed. If the inner layers are removed, the whole adrenal cortex can regenerate from the outer layer. Obviously, if stress causes cells to multiply and differentiate, cells are disappearing from the inner layers.

When I was in graduate school, immunologists were aware that new cells were continually appearing in the thymus gland, but the gland didn't get bigger, and there was no visible trace of dying cells. At that time, it was considered a major puzzle, but gradually it came to be understood that a special kind of cell dissolution (called apoptosis) was occurring that accounted for the missing cells.

In the testes, apoptosis or cell dissolution is always occurring, even though sperm cells are being produced and leaving the organ.

In the ovary, "waves" of egg cell degeneration are constantly taking place in young women. Radioactive labelling that has been used to argue that egg cells aren't being replaced seems to show that there is continual cell division in all the other ovarian cells. Interestingly, those researchers didn't seem to be interested in this apparent regeneration of the other parts of the ovary.

Apoptosis always seems to be part of a shaping process of the organ in which it occurs. Regeneration provides new cells, apoptosis recycles the substance of a certain fraction of the tissue's cells. We are just starting to notice that various hormones inhibit or promote apoptosis, and so participate in the "shaping" of the organism. In many systems, it seems

that the need for a cell type or function calls it into existence, while idleness makes a cell susceptible to dissolution.

I have been referring to the "pituitary gonadotropins," and deliberately avoided referring to them as LH—luteinizing hormone—and FSH—follicle stimulating hormone—because their names reflect a theory of what they do. In some textbook descriptions of testicular function, for example, it has been said that LH produces testosterone, and that negative feedback from testosterone suppresses LH, while FSH governs the formation of sperms. That description is completely worthless, and probably was largely built up by analogy with their supposedly neatly divided functions in the ovary, reflected in their names.

These gonadotropins participate in the development, maintenance, and functioning of the ovaries, and their effects depend on their timing, their balance with each other and with the steroids produced by the ovaries in response to their stimulation, and their actions are modified by many other factors, ovarian, nervous, pituitary, uterine, and immunological. During youth, the system functions in a coordinated way, with ovulation as a consequence. During aging, the crucial changes appear to be a decreased ability of the ovary and the brain to produce progesterone. Thyroid hormone, cholesterol, vitamin A and efficient cellular respiration are essential factors for synthesizing progesterone. Accumulated iron, unopposed estrogen, and impaired use of cholesterol and oxygen are factors known to contribute to the widespread and variable damage to the system of coordination.

Two things can cause the pituitary to secrete excessive amounts of the gonadotropins: A deficiency of the steroids, and damage to the steroid sensing nerves that regulate the pituitary. When an ovary is moved (transplanted into the spleen) so that its hormones are destroyed before getting to the brain, there is hypersecretion of gonadotropic hormone,[7–9] and tumors develop in the ovary. The interpretation, that hypersecretion causes the tumors, is supported by other observations, e.g., that removal of one ovary increases the chance of developing a cancer in the other ovary and that prolonged use of estrogen (known to create the conditions for later hypersecretion of gonadotropin)[3,4] increases the risk of ovarian cancer after menopause.[10]

Psychologists have noticed that naming an object according to a certain function often limits the way people will be able to use it. This happens in science. If we know one function of a substance, and name

it for that function, we will find it harder to think of its other possible roles. Hans Selye argued that steroids, for example, should be named according to their place of origin, rather than by a single aspect of their function. I think this applies even to the phrases "male hormone" and "female hormone": it's better to think of them in terms of their origin, and not to count on them to promote femininity or masculinity.

A note about "the female hormone." In the absence of the testicular or "male" hormones, animals differentiate as females.

Progesterone is an anti-androgen, and blocks testosterone's effects. When testosterone is given to newborn or very young rats, it sets up a male pattern of hormone development, but if progesterone is given at the same time, that doesn't happen. Progesterone prevents the differentiation away from the basic female path into the male specialization. Later in life, a deficiency of progesterone in a woman can again lead to masculinization of some features, such as musculature and facial or body hair. When progesterone is given to men in large doses, it blocks various typically male processes, such as growth of whiskers. In the brain, it has a protective function in both sexes.

Estrogen promotes cell division, and is involved in essentially every tissue, in both males and females. If it is to be called a "female hormone," maybe it also has to be called "a male hormone." It does have to be present for breast development, though it is just one of many factors. In this instance, it is contributing to feminization. In other instances, it seems to contribute to virilization.

At menopause, estrogen excess can promote the production of androgens, in the absence of progesterone, which tends to defeminize the woman. This is often a result of stress, and sometimes is a consequence of hypothyroidism. In situations of this sort, estrogen is seen not to be a feminizing hormone; it is unable to neutralize the male hormones the body produces in response to the estrogen excess.

Currently, estrogen marketing emphasizes appearance and the danger of osteoporosis. Evidence occasionally turns up implicating estrogen in thinning of the skin and bones.[11]

Aspects of Wholeness

Townsend Letter for Doctors, October, 1990

> "That a meeting-point between Biology and Physical Science may at some time be found, there is no reason for doubting. But we may confidently predict that if that meeting-point is found, and one of the two sciences is swallowed up, that one will not be Biology."
>
> — J. B. S. Haldane

HOLISM is the observation that, although natural objects can be resolved into their parts, the parts are to some extent shaped by their participation in the whole object. For example, in organic chemistry it is recognized that the reactivity of an atom or radical is modified by adjoining parts of the molecule, by the solvent, etc. Holism would never have been named, except that it is so common in our scientific tradition for someone to say "We know all there is to know about the parts (atoms, surfaces, fields, genes, etc.), so we can foresee the result of their combination." Good engineering involves knowing the properties of the materials so thoroughly that accurate predictions can be made about their behavior in new structures, but good science requires a willingness to accept the unpredicted when it occurs.

Holism, or a non-dogmatic attitude toward the world, recognizes individual uniqueness, rather than averages, and is likely to look for complex causes (especially environmental influences), rather than too easily ascribing traits "to the genes."

Historically, a reluctance to distinguish our present knowledge from possible knowledge, and to distinguish our definition of something from its real existence and fullest potential, has characterized most of the people who oppose holism, and call themselves reductionists. Consciousness, perception, sensation, pleasure, and intention have often been omitted from the world described by reductionists. If we are going to understand life and its possibilities, then it seems that we should begin with an appreciation of its "liveliest" aspects, as an essential dimension

of our thinking, even if we are going to work with some of its relatively inert aspects, such as viral genetics.

The relation of energy to structure is, I think, the central question of biology. (The importance of the same question for the physical sciences might indicate in a rough way how Haldane's predicted "swallowing up" might occur.) The ideas of resonance and hysteresis, which are only vaguely defined in physics, have to do with the interaction of energy and structure on various levels of complexity and organization, and are examples of physical concepts that can gain meaning and clarity from biology. When energy flows through matter, order accumulates (as a result of resonance and hysteresis, for example), but we hear so much about "entropy," "randomness," and "symmetry" that we forget most of the formative processes in the material world.

Human (and ecological) health obviously should have the benefits of holistic science, but the actual situation is that biology and medicine have become very product-oriented, and holistic considerations are increasingly left to a variety of "fringe" occupations. Many of these alternative approaches are concerned with the idea of "energy" as the key to health, but in general they lack simple and effective methods for optimizing biological energy, and often use counter-productive methods. In the following pages I will show how some of the most important achievements of ordinary science can be retrieved from the distortions of the medical promoters, and made available for holistic use, that is, for appropriate use.

Non-Genetic Biology

The word, "gene," itself contains an ideology, since it implies origin, or genesis, though its main meaning is something like "a unit of continuity." Building on the word's connotation, dogmatic geneticists explicitly stated their "central dogma": that information flows only from DNA to RNA, and only from RNA to protein. When Temin and Baltimore described the "reverse transcription" of DNA from RNA, all of the professional biologists I talked to said flatly that they didn't believe it was possible. Even when no one was threatening the addition of "information" to the chromosomes, the dominant belief among biologists was that development was closely controlled "by the genes," because the body owes its genesis to the genes. Intelligence, body proportions, and senescence

were said to be "specified" or "governed" or "programmed" by the genes. The "congenital" condition was often taken as the "genetic" condition. Textbooks said that the maternal influence was only "genetic," because the fetus was "insulated" from events in the mother's body (just as the "germ line" was isolated from events in the rest of the body). Although many kinds of experiments showed both prenatal and transgenerational influences of the environment on intelligence, body proportions, and rate of aging, the genetics-reductionist school ignored them, and defined themselves as the only scientific school of biology.

Mechanisms of Aging

Professor Soderwall and his students at the University of Oregon had shown that the corpora lutea (areas in the ovary which mainly produce progesterone) appeared to fail in aging hamsters, and that vitamin E supplements could extend fertility by a significant amount. His group showed that "aged ova" were not responsible for infertility, but rather that the uterine environment was not suitable for implantation. Soderwall had also demonstrated that excess estrogen could cause failure of the pregnancy at any point, from failure of the embryo to implant, to resorption of the fetus at a late stage of pregnancy.

Although I had investigated the association of estrogen with cancer, and knew from my own experience with migraines that stress, diet and hormones interacted in powerful ways, when I began to investigate the oxidative metabolism of the uterus I didn't realize that it would involve a convergence of several of my main interests. I was familiar with Otto Warburg's famous idea that cancer is caused by a "respiratory defect," and I knew that aged tissue had a diminished respiratory capacity. The textbooks indicated that estrogen deficiency and "aged ova" were responsible for senescent infertility. I found that the uterine endometrium of old animals often consumed oxygen at a high rate, and showed other signs of being under the influence of excessive estrogen. As I tried to understand this, I saw that several things could contribute to a high rate of oxygen consumption. Either too much estrogen, or too little progesterone could have the same effect, since it is the ratio between these hormones which controls their effects. A vitamin E deficiency increases oxygen consumption, and too much unsaturated fat has the same effect. In a vitamin E deficiency, unsaturated oils are oxidized in a way that

produces "age pigment," also called ceroid pigment or lipofuscin. This pigment consumes both oxygen and fuel, but produces no usable energy. Estrogen excess synergizes with a deficiency of vitamin E to intensify the formation of this pigment. Partly, this might be because estrogen is a powerful stimulant of iron absorption, and iron is involved in the peroxidation that produces the pigment. But low oxygen concentration is what causes the iron to become active in peroxidation, and estrogen acts in several ways to decrease the availability of oxygen.

The way in which estrogen prevents or terminates pregnancy seems to be by causing the uterus to consume oxygen at such a high rate that there is no oxygen available for the embryo, which has a high requirement for oxygen beginning on the day that it normally implants. The chronic or cumulative effects of estrogen, leading to formation of lipofuscin, happen to act in the same direction as estrogen itself, causing oxygen to be reduced, especially in the uterus, but in all other tissues, too. Estrogen excess can also destroy the corpora lutea, interfering with the production of progesterone. Progesterone's effect in pregnancy is to assure the availability of oxygen and nutrients for the embryo, but it also has the general effect of inhibiting the formation of lipofuscin, and of other aging signs, by improving metabolic efficiency. (Progesterone is unusual among the anti-stress steroids in having no harmful side-effects.)

Although my work confirmed the other research that had been done in Soderwall's lab in the preceding 25 years, the idea that estrogen's influence appears to increase with aging, and even to contribute to the process of aging, was contrary to the doctrine that has been promoted by the pharmaceutical industry. Nevertheless, as I read more, I saw that there was really no evidence contrary to what I had seen in my own work. What existed was a web of interpretation which existed to sell estrogen treatments. Even the fact that estrogen causes abortion was "ignored," very consciously, until the industry had fabricated a more acceptable rationale with which to sell its "contraceptive" pills.

The idea of many factors acting in the same direction, and tending to have a cumulative effect, seemed to me to have a general biological significance. It seemed to be part of the answer to the question of what it is which is lost, or accumulated, during aging, which accounts for the decreased ability to adapt to the changing environment. It seemed to say something about the nature of Warburg's "respiratory defect" in cancer.

The thyroid hormone, which governs respiration, is suppressed by estrogen, and by unsaturated fats. The wasteful metabolism of estrogen dominance tends to use up glucose, and is likely to activate the stress hormones, including cortisol.

The main features of aging can be produced directly by administering excessive amounts of cortisol. These features include atrophy of skin, arteries, muscle, bone, immune system, and parts of the brain, loss of pigment (melanin), deposition of fat in certain areas, and slowed conduction velocity of nerves. The physiology of aging (especially reproductive aging) overlaps the physiology of stress.

Puberty and Aging

Many studies have demonstrated that puberty seems to trigger the mechanism of aging, and the idea of a "death hormone," located in the pituitary gland, has been suggested. Many degenerative diseases develop under the influence of excessive estrogen and cortisone (and as a result of the many metabolic changes which follow exposure to those hormones). Many of these diseases, especially those which appear after puberty and are more frequent in women, can be treated very effectively with the anti-estrogen and anti-stress hormones, such as progesterone.

Hans Selye pointed out that estrogen treatment mimics the first, "shock" phase of the stress reaction. An excess of estrogen (or any stressor) causes the pituitary to secrete prolactin and ACTH, and both of these hormones act on the ovaries to stop progesterone production, and contribute in many other ways to the process of atrophy. ACTH, of course, stimulates the secretion of cortisol. The removal of the pituitary obviously isn't a practical way to delay senescence, but protection against the "death hormones" can be achieved to some extent by altering the diet to minimize the effects of estrogen and cortisol.

Historical and demographic studies show that certain conditions affect the age at which puberty occurs. Ashley Montague has argued that we need more neoteny, that is, that we should try to preserve and to extend our youthful functions, because those are our most human qualities. If we can generalize from animal studies, delaying puberty could increase brain size and longevity, improve intelligence, decrease violence, and even make people physically more attractive (the "cute puppy" appearance is largely a matter of brain size in relation to the size

of the face and body). I think this will be the next step in human evolution. Just as nurturing, stimulation, and freedom promote improvement in the function and structure of the brain, cruelty and oppression act in the opposite direction. If puberty is delayed, then the importance of a culture which supports curiosity, exploration, play and sensuous pleasure seems obvious.

The physiological age of the parts of an organism depends in some way on the developmental stage of the whole organism. This contradicts the reductionists' idea that cells or tissues have an "intrinsic" lifespan which will cause them to deteriorate after a certain limited number of divisions. When pieces of breast tissue or skin were repeatedly transplanted from old animals to young animals of the same (syngeneic) strain, they were still in good condition after ten "life-times," and their survival was apparently limited only by the necessity of trimming them each time they were transferred, to make sure that no host tissue was transplanted with them. When old rats were grafted onto young rats, the old member of the pair lived to twice the expected age. Recently, young female mice were grafted onto old females, to investigate any hormonal factors in aging. The ovaries of the young animal appeared to age, and its production of progesterone decreased.

This kind of evidence (and the simple observation that the cells in skin and intestine undergo thousands of divisions in an individual's lifetime) strongly favors the idea that a systemic energy problem is involved in aging.

Energy and Evolution

When mammals and birds achieved the ability to sustain a high metabolic rate by keeping their bodies at a steady, fairly high, temperature, their "food chain," based on photosynthesis, consisted of organisms that generally lived at a lower temperature.

Sugars, proteins, and the saturated fats produced by warm organisms can be eaten by warm-blooded animals with no particular side-effects. Organisms that live at low temperatures, however, contain unsaturated fats. The consumption of large amounts of unsaturated fats lowers the metabolic rate, and accumulated unsaturated fats are susceptible to a spontaneous and toxic form of oxidation. (The toxic effects include damage to the respiratory apparatus and to the circulatory and immune

systems, increased rate of aging, and cancer.) These "low energy" foods in effect counteract the evolutionary achievement of a high metabolic rate. Several studies show that decreased consumption of unsaturated fats can delay puberty. Other studies show that an excess of unsaturated oil in the mother's diet can damage the development of the fetus's brain. The choice of foods which have less unsaturated fat tends to reinforce the achievements of evolution.

The seed oil industry has created a national phobia about the consumption of saturated fats and cholesterol, but there is no basis for the idea that those foods should be avoided. People with hypothyroidism are susceptible to heart disease, but their elevated blood cholesterol becomes normal when their thyroid function is restored. The body's highest concentration of cholesterol exists in the brain. The level of cholesterol in the blood strongly influences the production of the protective hormones, such as progesterone. The brain contains by far the body's highest concentration of these hormones.

In the winter and at night the respiratory energy producing system is damaged, and the protective hormones decline, and the harmful stress hormones increase. The immune system becomes less active, and mortality increases. Although ultraviolet light interacts with unsaturated fats in the skin to accelerate aging[1] and to produce cancer, ordinary visible light has several beneficial effects in animals. One effect is the "regeneration" of the enzyme SOD (superoxide dismutase), by causing its copper atom to be re-attached to the protein. Light also increases the activity of normal respiratory enzymes, and tends to normalize (or maximize) the production of hormones, including progesterone and thyroid. Animal migration to reproduce in regions with longer days is a way to benefit from this energy-promoting action of light. In adult birds, the increase of hormones in the spring causes the growth of new brain cells in the area that controls their singing. (In humans, the space inside the cranium keeps increasing into old age, and the amount of DNA in the brain also keeps increasing with age, but it has been assumed that such changes in adult brains result from an increase in the size of nerve cells, and an increase in the number of connective tissue cells, rather than from a continuing increase in the number of nerve cells.) I would expect an increase in the temperature of the earth, and increased use of artificial light (or migration) to lead to a prolongation of youth and the development of better brains.

Pollution

Besides the distortion of our food supply by the propaganda of the seed oil industry, there is increasing contamination of our food supply by heavy metals. Lead, for instance, has been spread everywhere, largely as a result of its use in leaded gasoline. Food additives are often contaminated with heavy metals from the sulfuric acid used in their manufacture. Practically everyone knows about the famous experiments in which food restriction increases the longevity of animals, as if eating were toxic. But removing toxic heavy metals from the food, without restricting the amount of food eaten, has had the same life-extending effect in experimental animals.

When estrogen is elevated (as at puberty, or in pregnancy, or with medical estrogen treatment) the absorption of iron is stimulated. During aging, the body's load of iron increases, especially if there is a deficiency of copper, and the body's content of copper decreases with age. Copper is an essential component of cytochrome oxidase, which has the crucial last position in the mitochondrial respiratory system. Copper is a component of the cytoplasmic SOD enzyme, which decreases with age. Ceruloplasmin, a major copper-containing protein, helps to keep iron in its safe oxidized form. Copper is involved in the production of melanin (itself an antioxidant) and elastin. The loss of melanin, elastin, and respiratory capacity, which is so characteristic of senescence, is also produced by excessive exposure to cortisol.

The protein, metallothionein, is rich in sulfhydryl groups, which bind heavy metals. It is assumed that this protein helps to detoxify and eliminate the toxic metals. This protein is induced by exposure to either a heavy metal or cortisol. A larger amount is produced in response to the combination of heavy metals and cortisol, than by either alone. Since copper, like the toxic metals cadmium, lead, mercury, and silver, reacts strongly with sulfhydryl groups, the body is likely to lose some copper when it is subjected to heavy metals or cortisol. I think this chronic loss of copper accounts for the obvious features of aging, such as loss of elasticity of the skin, lungs, and blood vessels, the depigmentation (demelanization) of skin, hair, and (in Parkinson's disease) substantia nigra, and for the decrease in respiratory capacity. The replacement of the copper by iron (and the loss of the copper-enzymes which protect against iron-catalyzed free radicals) probably accounts for the increased

formation of lipofuscin during aging. When copper-dependent mitochondrial respiration fails, lipofuscin has the ability to sustain energy production through glycolysis (by keeping the coenzyme NAD, nicotinamide adenine dinucleotide, relatively oxidized), so it is possible that lipofuscin is a primitive sort of defense against stress.

In animals, copper supplementation can restore natural color to white hair, and in one experiment, it increased longevity. At present, there isn't enough knowledge about the safety of different ways of administering supplemental copper. It can be toxic, and it oxidizes other nutrients. Besides choosing foods high in copper and low in iron and other heavy metals, other dietary choices which support thyroid function will tend to promote the retention of copper. Other dietary practices can minimize our production of cortisol (e.g., combining fruits and protein, since protein foods lower blood sugar and stimulate the secretion of cortisol).

Self-Regulation

Physical science provides a much richer picture of the qualities and potential of the material world than geneticists recognize. Even many physicists don't recognize the richness implied by the body of experimental results in their field. Many well-known physical scientists have had relatively holistic attitudes (e.g., J. C. Bose, Michael Polanyi, B. V. Deryagin, Frederick Soddy, V. I. Vernadsky). A rich view of physics has much to offer to biology. However, when I say that a holistic view of biology is open to using physics and chemistry, as well as ecology, history, and cosmology, to achieve an adequate understanding, I should mention that there is a school of weird (immaterial and "quantum" centered) physics which is presenting itself as a holistic world-view. To them, I think Einstein's remark still applies: "You believe in a dice-playing God and I in perfect laws in the world of things existing as real objects…" Elsewhere, Einstein observed that an object's fields amounted to an extension of its material substance, i.e., he preferred to materialize fields, rather than to dematerialize things, as some of the popular philosophers of physics do.

The orderly, epitaxial growth of crystals has been shown to occur across the thickness of a plastic film. A detailed study of this sort of long-range ordering process was made by Alexander Rothen. He was able to

demonstrate biologically specific adsorption at relatively great distances. Many other types of research in adsorption fields and long-range order make it clear that the interactions of atoms and molecules in cells needn't be governed by either direct contact or by random motion. When cell components are rearranged, they return to their normal position in relation to other components, revealing a great capacity for self-assembly or self-ordering.

The medical tradition of naturopathy recognizes a great capacity of the body for self-regulation and self-healing. I think these attitudes can be usefully expanded now, in the light of new knowledge about energy and structure. On the short time scale in which we think about the health of an individual, and on the transgenerational scale relating to having healthier, more intelligent children, and on the evolutionary time scale, I think we can see a tendency, not just to preserve homeostasis, but to move upward in energy and greater generality of structure and function. To provide more energy and scope for using it stimulates our ability to use energy meaningfully.

Some Implications

There is considerable flexibility in living organisms, and in higher and lower levels of organization, and we can see some of the ways in which structures of different complexity accommodate themselves to the surrounding conditions of energy and structure.

The conditions under which the brain develops, including gestational support and the later nutritional-hormonal-behavioral conditions, the degree of stress and stimulation, contribute to the brain's structural complexity and metabolic energy use, and to the organism's ability to cope successfully with the environment.

Vicious circles of physiology often stabilize an organism on a low energy level, which may involve disease or rapid aging.

The existence of a few systems of positive feedback (self stimulation), however, indicates that in our fundamental structure we are biased in an expansive, upward direction. Progesterone (and its precursors, pregnenolone and cholesterol) and thyroid hormones participate in some of the important positive feedback systems, involving energy production, stress resistance, and brain growth.

In therapy and in everyday living we can try to protect and promote our energy-producing and energy-using systems by seeking the stimulation, the conditions of light and temperature, and the foods that are appropriate for our evolutionary level.

Asthma and Metabisulfite

Townsend Letter for Doctors, June, 1986

An asthmatic friend of mine had several experiences of getting sicker when she was medicated for asthma. While hospitalized, her doctor insisted on giving her Alupent. After she left the hospital, she showed me the Alupent label and asked if I knew why it would make her so sick. The label listed metabisulfite as an ingredient. Since this substance is known to cause trouble in asthmatics, it is very odd to find it in an asthmatic drug.[1] I don't find metabisulfite listed as an ingredient of Alupent in the PDR or other drug manuals, and the physicians I have mentioned it to were surprised. Sudden death from "paradoxical bronchospasm" would not be paradoxical at all.

Biological Balance and Addictions

Townsend Letter for Doctors, June, 1991

A good salesman knows how to get onto waves of rising enthusiasm. Intuitively, politicians, cult leaders, and scientists use the same process. The quick rewards of joining a rising tide reinforce the conformists' efforts, and thought needn't go much beyond "this must be true, because it works for me."

In the early 1950's, David Reisman discussed the idea of counter-cyclic activity in economics and culture, as an error-balancing technique. One of the simplest ways to evaluate the meaning of a cyclic process is to see what happens if it is damped or opposed, and to compare these results with an alternative amplification or reinforcement. The technique is useful biologically, as well as socially: pharmacologists have used the method for centuries, and theories of medicine are based on either damping or intensifying the wave-like processes.

Withdrawal from an addictive substance involves a physiological swing to a kind of "opposite pole," or nadir to the zenith of the drug's action. As no drug has just one effect, the deformation of physiology remaining when the drug is removed will not be a simple matter of a single "receptor" molecule. Physiology compensates continuously to maintain balanced functioning in the presence of a great variety of drug-like substances in our diet. When the diet is changed suddenly, eliminating alcohol or caffeine or other biologically active substances, our compensatory counter-cyclic adjustment is revealed.

The return to a physiologically balanced state requires many changes, and these occur at different rates. (The physiology involved in any organismic function consists of overlapping layers, each of which can work alone to some extent, and dysadaptation can affect the different layers—e.g., hormonal and neural—in different ways. And within a given regulatory "layer," such as the autonomic nervous system, there are various kinds of adaptive processes, including adjustment of energy charge, rate of "firing," thresholds, synthesis, and growth.)

It is important to think concretely about the processes in "recompensation" or restoration of balance. Some of the processes we should consider in relation to addiction are: tissue energy charge, metabolic detoxi-

cation and elimination, permeability and barrier functions, excitation-inhibition, and poorly compensated stress reactions.

Probably the biggest error in our popular culture of addiction is the idea that craving is triggered by the presence of the substance in the body, and that cleansing the substance from the body will stop the craving. This idea has become quite a cult, with ramifications into theories of obesity, allergy, sexual dependency, and violence. The common element in these widely promoted cultish systems is a distrust of the organism, a body-rejecting attitude that craving is necessarily bad, leading to a blurring of the difference between need and addiction. Cleansing the offending substance from the body to stop the craving suggests that the clean and pure person is without desires. Opposing this other-worldly doctrine is the fact that desires reflect needs, though seldom in a fully rational way. The fact that something makes you feel better, and that you feel worse when you stop using it, shouldn't be taken as evidence of its "addictiveness," but many people feel that way about thyroid hormone, coffee, vitamins, and even the most ordinary foods.

The fact that a taste of chocolate can provoke a wild lust for more chocolate, or that one cigarette renews the addiction, does not mean that the presence of chocolate or nicotine in the blood creates a craving. Rather, it is that an organism in an unstable state perceives the availability of something which promises to partially restore the desired stability. It is obvious that smoking cigarettes is not a good way to achieve the needed stability but this observation can't be generalized to the craving for potato chips, or coffee, or the multitude of other things that people often crave. There is often an easily discovered reason for cravings, and it is more fruitful to suspect that all cravings have a rational basis than to accept the Calvinist or Buddhist idea that desire itself is bad.

The availability of energy is central to our stable functioning, and the need for energy powerfully modifies our functioning. For example, as hunger increases, the brain's interpretive system changes in a way that causes increasingly unfamiliar things to be considered as possible food. The "spreading excitation" that leads to this extended search probably occurs in relation to needs other than hunger, and could lead to experimentation with drugs and to other activities that give some indirect satisfaction. Obsessive and compulsive patterns can sometimes be resolved by assisting the brain's energy metabolism, for example with a supplement of magnesium and thyroid.

But even hunger itself has such ramifications—protein deficiency, salt deficiency, hypoglycemia, elevated adrenalin and cortisol and growth hormone, for example—that a great variety of things could give partial satisfaction. Alcohol can make a powerful and positive contribution to nutrition by sparing protein, and by modifying nutrition-related hormones. (Although some of this work has been published in the *Journal of the American Medical Association*, the stigma attached to alcohol has prevented its adoption as a most useful drug/nutrient, even in terminal cancer patients, where its promotion of immunity could have great value. The abusive stigmatizing of useful substances is an example of unhealthily exaggerated social cycles.)

Behind alcoholism, it is common to find nutritional and endocrine problems, as well as emotional or situational problems. For example, a man who had been unhappy with his work and had struggled with "alcoholism" for 13 years, gave me the impression of someone lacking the basic hormone precursor, pregnenolone. A few minutes after he took 100 mg of pregnenolone, his depression and anxiety disappeared. Later, he said "that's the feeling I've been trying to get from alcohol, but it never worked." Pregnenolone, more powerfully than alcohol, lowers cortisol while stabilizing other systems. Its highest concentration in the body occurs in the brain, and its level declines sharply with aging; it very likely makes a large contribution to the adaptiveness and sense of well-being which are characteristic of healthy young individuals. In healthy young people or animals, additional pregnenolone has no detectable effect.

"Agitated depression," which is common in old age, is a common symptom of withdrawal from a variety of addictive substances. I suspect that agitated depression, or anxious depression, is a stress syndrome that makes ordinary adaptation difficult. The inability to cope with everyday problems often precedes experimentation with drugs. Low energy and high anxiety can lead a person to use either stimulants or sedatives, or both. Curing the initial problem should make withdrawal from many substances easier, though most of my experience relating to "addiction" has been with "alcoholism."

In 1979, I was thinking about steroid anesthesia, and decided to test whether the newly discovered "opiate receptors" were involved. Naloxone, the anti-opiate, didn't seem to block progesterone anesthesia, but I was still convinced that there was a connection. I think of progesterone as acting at a deeper or more general level, which could allow synergism

between opiates and progesterone, without naloxone's blocking the effect of progesterone.[†]

By chance, a musician who said he had been using heroin and alcohol for 40 years asked if I could help him sober up for an important job that was to begin in a few days. He said he had been continuously drunk for 6 weeks. He brought a quart of beer with him when he came to the house, and since we were having a holiday dinner, he had a chance to keep drinking wine when his beer was finished. At bedtime, I told him about my inconclusive experiments with progesterone, and described the other effects of the material, including its brain-quieting and anti-toxic, anti-stress effects. He took about 100 mg then (in vitamin E), and took the rest of the bottle to bed with him. Since he had serious cirrhosis of the liver, I explained that he should also take triiodothyronine, since this active form of the thyroid hormone is formed mainly in the liver, and I suggested that his nearly destroyed liver was probably making very little.

He got up around 8 o'clock the next morning, and was smiling and very happy looking. He said he had never had this experience before, of waking up without a hangover after heavy drinking. He had consumed so much of the progesterone that I repeatedly told him to be aware that it could interfere with his sexual function by blocking the effects of testosterone. He stayed alert and sober, and proceeded with his performances. He took about 30 g of progesterone in vitamin E over the next several months, and said his sexual functioning was perfectly normal. He took 50 μg of Cytomel morning and night, and his doctors gave him a few injections of magnesium. His doctors noticed that his liver was getting smaller, and about a year and a half later they said it was normal, without cirrhosis. (Since then other people have noticed similar effects on inflamed and enlarged livers, when taking progesterone with vitamin E and thyroid.)

Both progesterone and triiodothyronine have the function of increasing the tissue's energy supply, and in suitable doses can have a steadying, calming effect. While many people think of thyroid as a kind of stimulant, because it can cure the coma or lethargy of myxedema, this is a very misleading idea. In hypothyroidism, the brain exciting

[†] The systems which respond to valium and atropine are the places that I would want to look for clues to progesterone's effects on addiction.

hormones adrenalin, estrogen, and cortisol are usually elevated, and the nerve-muscle relaxant magnesium is low. Normal, deep sleep is rare in a hypothyroid person. The correct dose of triiodothyronine (the active thyroid hormone) with magnesium is a reliable treatment for insomnia, cramps, and anxiety, whether these symptoms are caused by fatigue, or aging, or alcohol withdrawal.

Aging, stress, and heavy consumption of alcohol increase the permeability of the intestine, causing increased absorption of microbial toxins. Laxatives, carrot fiber (not carrot juice), activated charcoal, and a small amount of sodium thiosulfate decrease the formation and absorption of toxins, increasing the organism's adaptive capacity. Belladonna can improve the bowel's function if there are spasms during drug withdrawal.

Camphor, adamantanamine (amantadine, Symmetrel), and "local" anesthetics taken systemically, can help in withdrawal from stimulants. The conventional (200 mg) dose of camphor and adamantanamine shouldn't be exceeded. (The hormones thyroid, progesterone and pregnenolone alone are sometimes enough.)

Smoking is probably the hardest addiction to break, but careful use of nicotine gum with belladonna (to block some of the circulatory effects of nicotine) can allow a person to avoid the worst toxins of the smoke while overcoming the behavioral habit of handling cigarettes, without having to simultaneously modify the chemical addiction. Caffeine[1] and vitamin A are very protective against cancers, including those induced by smoke. Progesterone and pregnenolone both have anti-toxic (or "catatoxic") effects, though their effects on nicotine craving are slight.

Our society's mystique about drugs makes it hard for people to rely on their own judgment and experience. If they want to try to feel better, aspirin, coffee, tobacco and alcohol are normally the only drugs they have to experiment with. Too many physicians think of "euphoria" as an undesirable side-effect of certain drugs, and are likely either to recommend stoicism, or to mechanically prescribe one of the standard mood altering drugs.

Ideally, a physician should view unhappiness and the feeling that life is getting too hard to handle, as a biological problem to be explored in cooperation with the patient. If circumstances are responsible, and can be changed, the biology will take care of itself.

The institutions and cults that have grown up around "treating addiction" are not so different from the cults and institutions (including

the pharmaceutical industry) that surround the use of drugs. Rationality and concern for the full range of real needs of people are likely to be ignored when stereotypes and ideologies can be used so profitably.

Dealing with addictions as having (directly or indirectly) to do with real needs can help to remove some of the unnecessary guilt and anxiety associated with addiction. This makes it easier to find out what is really needed to move toward a stable and balanced physiological state. As simple as it is to recognize addiction as a process of biological adaptation, there are many tricks for evaluating and facilitating the process, that can be discussed in more detail later.

Painters and musicians have sometimes said that they use alcohol or other drugs to help them find their "own way." Moving against the tide of the culture is an adaptive effort, and they find some neurological support in drugs. They are right in struggling against the current of imbecile conformity to find some creative truth, but there are better ways to sustain our energy and adaptive capacity. In some cases, good food and social fairness are enough to enliven people so that drugs are not attractive, and in other cases a more specific biochemical/energetic approach is needed.

Bowel Toxins Accelerate Aging Process

Townsend Letter for Doctors, February/March 1991

THE gerontologist, V. V. Frolkis, recently found that mice lived 43 % longer than animals on the standard diet when they periodically had activated charcoal added to their food. This is the clearest evidence I have seen that "bowel toxins" make a major contribution to the aging process. Although I think carrot fiber would have a similar effect, there might be important differences in the substances bound by wet cellulose and by microporous carbon. Analysis of the substances bound to the charcoal after it has been excreted should give us important new knowledge about aging. Besides endotoxin, I think the charcoal might protect against microbial estrogen and glucocorticoids, carbon monoxide, cyanide, and unsaturated oils. Absorption of heavy metals is probably decreased by all types of "fiber."

While Boganmoletz and Metchnikof saw the bowel toxins as the factor which drove the aging process, I see bowel toxins rather as a relatively late-acting factor that accelerates a process which develops for other reasons. Once our detoxifying mechanisms begin to fail, bowel toxins pass the bowel with relative ease, and rapidly destroy the remaining systems of defense and detoxification. The altered hormonal environment and weakened digestion of an aging organism create a new balance between the animal and the bowel flora, sometimes allowing the proliferation of more toxic flora. The accumulation of iron and other heavy metals, and of unsaturated fats, and the progressive loss of copper under the influence of the stress of darkness, are probably the central events in the process of aging.

Brain Aging

Townsend Letter for Doctors, August/September, 1992

Elie Mechnikov, like Pavlov, built a broad understanding of the nature of animals from a basic study of the process of nutrition. He believed that in the development of an individual, and in evolution, there is an early stage in which a division of labor occurs, with some cells being responsible for movement, and other cells (the amoeboid phagocytes) being responsible for ingesting and digesting food. The nutritional function of these latter cells was the basis for building and shaping tissues, and as the complexity of the organism increased, the phagocytes remained central in the preservation of the integrity of the organism.

Some examples will illustrate the ways in which phagocytic white blood cells preserve integrity. In a wound, white blood cells arrive quickly. Foreign matter, such as bacteria, is ingested and destroyed. If the object is too large to ingest, the cells adhere to it, and seal it off. Other white blood cells participate in healing, wound closing, and scar formation. Damaged or virus-infected cells of the organism, or cancer cells, or "old" red blood cells are destroyed and removed. Tissue remodeling—ranging from the tadpole's shrinking tail to the reshaping of bone by osteoclasts—is handled by this sort of cell. (That is, removal, replacement, and alteration of tissue are handled by this system.)

The energy available to the white cells, and the condition of the various tissue cells, govern the processes of phagocytosis, healing, and tissue remodeling. Thyroid hormone and body temperature are important factors governing the activity of white cells. The rate of movement of white cells through the tissue is strongly dependent upon temperature[1] (with the rate increasing with an increase in temperature), and they are generally tolerant of very high temperatures.[2] The conditions governing resorption of the tadpole's tail are probably relevant to how white blood cells function in mammals. Either cold or hypothyroidism tends to suppress or delay the phagocytic activity in the tadpole tail. With an adequate temperature and thyroid hormone, the cells selectively remove the oldest cells first, indicating that they recognize cellular age.

Although Mechnikov believed that the phagocytes were responsible for the atrophy of aging, he also believed that bacterial toxins from the intestine dominated the aging process.

Bacterial endotoxin inhibits mitochondrial respiration, and this respiration is needed for the intramitochondrial conversion of cholesterol into pregnenolone. With aging, pregnenolone and its derivatives, progesterone and DHEA, decline sharply. The brain, the organ with the highest concentration of those stabilizing substances, has many systems for adapting to their decreasing concentration, but the immune system is probably less able to compensate for those aging changes.

The combination of an extreme decrease in concentration of the protective steroids in the brain, and impaired function of the phagocytes, might account for some of the features of Alzheimer's disease. In this disease, microtubules accumulate within nerve cells and other nerve cells die, leaving tangles of their axons, including microtubules. These cells are not removed, as dead cells normally are. Subnormal temperature and hypothyroidism probably contribute to the inertia of the phagocytes. (In mammalian cells, microtubules dissolve at low temperatures, and are stable at higher temperatures. Phagocytosis seems to depend on a functional microtubule system within the white cells.)

But the reason for the nerve cell's death, and for the tangles of filaments within living cells, seems to be a metabolic problem of the nerve cells themselves. A few years ago, there was talk of a similarity between the "amyloid" deposits, and the blood protein, pre-albumin. Since that protein transports vitamin A and thyroxin, I wondered about the possible effects of a vitamin A deficiency. Vitamin A regulates lysosomes, and so a deficiency might promote the accumulation of intracellular debris. It is an antioxidant, and so a deficiency might tend to induce the stress-hypoxia proteins, and it is used massively in the synthesis of steroids (for example, progesterone supplementation spares vitamin A). But possibly most important is the "de-differentiation" that occurs in many cells in a vitamin A deficiency. In the skin and mucous membranes, a vitamin A deficiency acts like an excess of estrogen, to promote the formation of keratin.

Twenty years ago, English researchers found virus-like shapes in the brains of old people, and suggested that senility might be caused by a virus. Later, one of them found that aged brain tissue was antigeni-

cally similar to scrapie-infected brain tissue from a young animal, and antigenically distinct from healthy young tissue.[3]

In size and over-all structure, keratin filaments are similar to the scrapie particles, and to the filaments that accumulate in Alzheimer's disease. I think of keratin as a protein made by a cell which has lost the energy to make more functional proteins. Normally, keratinized cells are formed by rapid cell division at a body surface, where little energy is available. In chronic vitamin A deficiency, the keratin-forming cells divide more rapidly than normal. Dandruff and the moist white equivalent of dandruff on mucous membranes, leucoplakia, are promoted by a deficiency of vitamin A, or an excess of estrogen. Radiation often causes a similar hyperkeratosis, probably by destroying vitamin A, and, like estrogen, by creating a respiratory effect.

I suspect that the plaques in Alzheimer's disease are the brain's equivalent to the plaques of leucoplakia, or of dandruff, and that the overgrowth of the glial cells is the result of the same tendency of cells to divide rapidly, while the non-dividing neurons accumulate an excess of fibrous proteins that can't be degraded.

In degenerative diseases, the stress- and age-induced accumulation of iron and other mitochondria-toxic material (e.g., calcium, aluminum, and lipid peroxidation products including age-pigment) and the failure of detoxifying systems make therapy with ordinary nutritional supplements fairly ineffective. Direct supplementation of the various natural protective substances (or their analogues) in addition to the protective vitamins (especially E) and minerals (especially magnesium) is more appropriate.

The supplementation of pregnenolone, etc., will allow dietary vitamin A to be spared for other purposes, including regulation of mitosis, differentiation, and oxidation.

GABA-related metabolites, such as GHB, butyric acid, succinic acid, and the butyrobetaines, have multiple protective functions, including promotion of respiration and pregnenolone synthesis, regulating gene expression, and reducing damage from glucocorticoids.

DHEA seems to be involved in various regenerative processes, and a deficiency of it is prognostic of increased probability of death from various causes, including cancer, heart disease, and AIDS.

Progesterone has the special status of being an essential nerve growth factor, and generally blocks the catabolic actions of the glucocorticoids

and estrogen, thereby protecting all tissues, from brain cells to white blood cells.

Thyroid hormone protects against stress and supports normal differentiation.

Short and medium-chain saturated fatty acids provide a safe source of energy, as well as having hormone-like and adaptogenic effects. The short-chain saturated fatty acids are important in regulating bowel flora. Mechnikov's idea of altering the flora with cultured milk was on the right track, but much more needs to be done on bacterial nutrition and toxin formation.

Can Some "Anomalous" Structural Interactions Be Explained by an "Excitable Ether"?

Multidisciplinary Research, Volume 4, Number 44, 1976

FIRST, I want to indicate that I feel an ether theory is philosophically desirable, as an affirmation of rationality and causality beyond even that of the "traditionalist," geometrizing Einstein. Subjectivism in physics is being carried to extremes, and it is time to make physics again a strictly objective science.

Dudley and others have given some very interesting arguments for ways in which the neutrino sea could account for physical events which have traditionally been described in terms of special "fields" and "spontaneous events." I suspect that many of the "anomalies" that have accumulated in recent decades can be accounted for by a similar approach, though at present (for most purposes) I would feel just as comfortable with the phrase "previously unsuspected general process or medium of interaction" as with the concept "neutrino ether."

Lenin's definition of materialism was "the belief that there is something beyond what is presently known." This belief, and its opposite, define the two kinds of science that have been described by Kuhn as "normal science" and "revolutionary science," respectively. Since "normal science" doesn't postulate a world beyond what is known, it is always satisfied with any tolerably consistent set of descriptions. "Normal science" is possible only in a culture which is committed to the metaphysics of idealism, as opposed to a materialism as defined by Lenin. Lenin's materialism incorporates an assertion of the reality of time, an assertion of matter as our future, our potentiality. From the objectivity of time, this materialism (which is dielectical, developmental, historical or temporal) is committed to the reality of causality. It gives us an approach to physics which is utterly different from the idealistic tendencies of Jeans, Eddington, Schroedinger and others who assert that beyond our knowledge there is nothing.

Two Hindu physicists (Bandyopadhyay and Chaudhuri) have suggested a way in which time, by altering the neutrino sea, would be responsible for the cosmic red shift, and also for an altered gravitational constant. This is a concrete way in which the ether concept is made to affirm the objectivity of time, of causal sequence.

N. A. Kozyrev has successfully predicted numerous physical interactions by introducing

> *into theoretical mechanics the principle of causality and directivity of time. Such a mechanics can be called "causal" or "asymmetrical" mechanics.*

Kozyrev recognizes "the inadequacy of the knowledge of the essence the casual relationships," and so can be said to be systematizing a "previously unsuspected process or medium of interaction" which participates in all events, without specifying all its properties. His theory, which began with his studies of the internal structure of stars (1948, 1950) and stellar power, led him to accurately predict the cardioid asymmetry of Jupiter and Saturn (and Earth), the internal heat of Jupiter and earth's moon, and the red flares on the moon, and to account for the southward deflection of falling objects recorded by Hook (1680) and Reich (1832). He reports that the effect of the causal transmission of energy upon measuring devices such as clocks diminishes with the first power of the distance, and is not affected by shielding. Each of these points—effect on clocks, proportionality to the first power of distance, and passing through ordinary "shielding"—recalls a variety of other experiments which have seemed to involve unusual interactions, possibly involving a "medium of interaction." I will mention a few in the following pages.

Before the first world war, the "best" physicists thought they knew enough about the electrical nature of matter to reject as "ignorant" a theory of multi-layer adsorption which proposed a potential which could extend into space from the adsorbing surface, even through layers of adsorbed molecules. Thus, Einstein and Haber humiliated Michael Polanyi, rejected his data and ridiculed the notion of an "adsorption potential," almost causing Polanyi to give up his scientific career. About 15 years later, Polanyi and London collaborated to show how electronic fluctuations could account for the adsorption data obtained by Polanyi. Still, for another 15 years no one was willing to oppose the earlier, prestigious but ignorant opinion of Einstein and Haber to use and evaluate Polanyi's isotherm, which turned out to be the most widely useful adsorption isotherm, though Polanyi's never won prizes, as did Langmuir's mistaken theory. In fact, nearly thirty years later (or nearly 60 years after Polanyi's humiliation) I have questioned "experts" on the

subject, and found that almost all of them consider Polanyi's isotherm to be "wrong" and of no use, though they are also ignorant of the data relating to it.

After completing his thesis, Polanyi turned most of his attention to other problems in physics, but kept encountering data which seemed to indicate a kind of "smearing" of energy over considerable distances. For instance, while Max Born developed the theory of crystal lattices, again on the basis of merely local atomic forces, Polanyi was observing domains of some sort in crystals which seemed to involve delocalization of forces over distances of about 2 or 3 millimeters. He believed that he demonstrated that defects strengthened crystals:

> *I was deeply struck by the fact that every process that destroyed the ideal structure of crystals (and thus reduced the areas which could be regarded as single molecules) increased the resistance of crystalline materials. This seemed to confirm the principle by which I explained the low resistance of crystals to stress and to refute the rival theory...*
>
> *Polanyi's principle for understanding the strength of crystals was that the energy required for producing the new surface formed by breaking the crystal would have to be supplied from the stress stored up on either side of the future break, in an area extending two or three millimeters in both directions of it.*

Other experiments, involving plastic deformation, hardening crystals by wetting a surface, deformation hardening in one direction, and "recovery" of crystals, even a study of friction, all tended to support Polanyi's idea of the spatial extendedness or delocalizability of the energy involved in the solid state. In form, they seem similar to the adsorption potential which had been conceived without knowledge of "the electrical concept of interatomic forces." About the same time he found that the rate of reaction of chlorine was too fast to be accounted for by the ordinary reaction kinetics. Born described his results as requiring that energy just jump through empty space, as if that were impossible. It is now commonplace to use light to catalyze a reaction such as polymerization, even using chemiluminescence as the source, but the data

Polanyi obtained again seem to have been forgotten, in favor of a free-radical chain reaction explanation of the chlorine reaction. Polanyi now considers the adsorption potential to be explained by "resonance between the polarization of electronic systems," but I suspect that a common denominator of some of his work was an idea of an "excitable ether," which he in fact used in at least one publication.

The common "inverse square" relationship geometrically suggests that the force is being distributed as if on the surface of a sphere: so it would seem reasonable for forces extending from flat or concave sufaces (as opposed to points, or single ions) to decrease less rapidly with distance. This is apparently the case in the adsorption experiments of A. Rothen, in which antibodies are adsorbed out of solution by a layer of antigens spread on a thin layer of metal deposited on a glass slide. The effect depends on a certain crystalline structure in the metal, and is destroyed by subjecting the slide to a magnetic field parallel to the surface. In a recent publication (Biophys. J., 1974) Rothen reported that the slides were gradually inactivated during the day, unless shielded by about 3 cm to 5 cm of lead, but that they tended to be reactivated at night, by 1 cm of lead. Irradiation with gamma rays also prevented daytime inactivation. The period of inactivation and its maximum degree were greatest in the summer, corresponding to the position of the sun. Although he suggested comic rays as a possible cause of this diurnal change ("It is most intriguing that comic rays may be able to favor one configuration or the other depending on the penetrating power of the rays"), those rays are so nearly isotropic that such an effect is unlikely. Rothen's work has attracted little interest (except for a recent thief, who visited him to learn his method and then claimed to have developed it himself), over a period of about 35 years, and one story is that, after he had demonstrated that the effect could be transmitted through a plastic film, someone reported holes to exist in such films. The criticism was incompetent, not only because numerous layers of antibodies could be demonstrated, but because it has been shown microscopically that epitaxial growth of crystals can extend through a similar plastic film—for example, condensing sodium atoms in the pattern of the underlying quartz crystal. The ordering process in the two cases probably has some similarity.

The heavy shielding used to block Rothen's diurnal effect is reminiscent of the many studies done by Frank Brown, showing that organisms

in sealed and electrically shielded containers responded to events such as sunrise, sunset (and, I think, even moonrise), the arrival of the sun at the zenith, etc. For example, potatoes respire more intensely, clams or oysters open their shells when the tide would be high (if the tide could come as far as Indiana), etc. John Ott has made similar observations, for example that a mimosa plant (m. pudica) would continue to fold its leaves at right even though isolated in a cellar under a cement roof; another experiment showed that a plant would respond to sunset and sunrise under a few yards of earth, but that when taken down to a depth of hundreds of feet in a salt mine, the response stopped. Brown's studies show that biological clocks are set by external cues. Ott shows that the balance of radiation is crucial. A French microwave expert has used a complex combination of frequencies to stimulate animals' immune systems; his belief is apparently that a complex substance, the organism, is tuned to a complex frequency. Something of this sort seems to be involved in the highly specific resonance of Rothen's adsorption experiments.

Dror Sadeh mounted a cesium clock on a truck, and left another in Washington, D.C.; when he was a few hundred miles north of Washington a discrepancy between the clocks developed, in which one of them appeared to be "red-shifted," or slowed. The effect began at sunrise, and continued for a few hours each day; I think a similar but smaller shift occurred with moonrise. Anything which could affect the vibration rate of cesium might also be the (seemingly non-electromagnetic) cue by which organisms set their "clocks." Incidentally, the experiment in which a cesium clock was flown around the earth to test the relativistic "twin paradox" would have presented the clocks with a different number of sunrises, and so might be taken as a test of Sadeh's principle, rather than of relativity. Since Polanyi's adsorption potential is in effect condensing the molecules of a gas as they approach a surface, it is not hard to see a similarity between Rothen's adsorption of proteins onto a plane surface being modified in a diurnal rhythm, and Sadeh's diurnal change in the vibration of cesium molecules.

It is know that a lead "roof" of about an inch thickness produces an optimum shower of particles when hit by cosmic rays. Neutrinos are known to be produced in the process, so if there were a diurnal change in the energy state of an ether (consisting of a neutrino sea) which was affecting the various vibratory (resonant) processes, adsorp-

tive processes (also a kind of resonance, since Rothen's adsorption of antibodies demonstrates specificity), and biological processes, a lead roof might noticeably alter the average neutrino energy, possibly accounting for Rothen's effects. The Anderson-Dudley effect, in which a surface (or solid-state domains) can alter nuclear decay rates suggests an interaction of surfaces with an ether, a "sub-quantum medium" or sub-quantum mechanical level, to use Bohm's terms. If surfaces act on nuclei through such a medium, then it is appropriate to consider such a medium of interaction in other situations which involve surfaces, long-range order, cyclic effects, etc.

In an old monograph on cosmic rays (1942) an experiment is described in which pregnant rabbits abort when placed under a lead roof, and other experiments showed cancer growth rate was increased by the lead roof. In Sciencia Sinica (1964-66) a series of papers describes similar experiments, in which a similar lead roof produced different cancer rates at different elevations, with differences also being produced by varying the thickness of lead. Rothen's effect might also vary with altitude. Recently (1975) it was reported that, contrary to the previous belief that the greater "radiation" at high elevations would produce more cancer, the cancer rate declines with increased elevation, even for melanoma within Texas, according to a cancer geographer in that state.

Since many ether studies (e.g., Miller's large series of measurements of light velocity at different elevations) suggest that the ether density varies with altitude, it would be interesting to compare the effect of elevation (and shielding combinations, including deep mines) with the diurnal effects, on many biological and physical systems.

The medium of interaction in some cases could turn out to be a property of the matter itself, without invoking an ether. Intermediate states of matter, such as liquid crystals, interact with energy in previously unexpected ways. But while remaining open to many new kinds of explanations, we should keep in mind that the right kind of ether theory might be able to explain various anomalies, while unifying physical theory—and possibly also chemical and biological theory, as Kozyrev mentioned in connection with his theory. Such an ether theory would probably be extraordinarily fruitful in terms of new observations and new technologies.

Chronic Fatigue

Townsend Letter for Doctors, July, 1994

A good thing about science is that even dull-witted people can make real contributions to knowledge, by working carefully and methodically. Science tolerates (but doesn't require) quite a bit of stupidity. But I am inclined to think that education (or training) in science is heavily biased toward stupidity. It is through education that the achievements of science become part of our culture, and our culture influences the future directions science will take. So, both science and our culture would be better off if we would habitually ask whether the scientist's basic assumptions are justified, what alternative explanations had been considered, exactly what is meant by a specific word, and so on. Such questions almost always reveal the most embarrassing weaknesses in a position that "almost everyone agrees is correct." In biology and medicine, it seems that nearly everyone explains almost everything with a few interlocking ideas: DNA, membranes, membrane pumps, membrane receptors and receptors for the DNA, and ion channels. A belief in the explanatory power of these ideas can convert an observation that bacteria behave a little oddly when they are given ethyl alcohol, into a publishable speculation on the "molecular biology of membranes."

When the cells of fat, or depressed, or tired people are found to be in a low energy state, defective membranes, or membrane pumps or membrane receptors are often mentioned. Since phospholipids, which contain fatty acids of various degrees of unsaturation, are believed to be a major component of "the membranes," some people argue that eating more of the polyunsaturated fats will help to build new membranes, or to increase the "fluidity" of the membranes. If it is suggested that the cells should be producing more energy, some people suggest that, since the "mitochondrial membranes" are highly unsaturated, eating more of the polyunsaturated fats will help them to produce more energy.

A crucial enzyme in the mitochondrion is cytochrome oxidase, which reacts directly with oxygen, completing (or beginning) the process of chemical respiration. It is this enzyme (which is most sensitive to cyanide) which appears to be a "choke point" for energy production in various situations. Learning how to preserve and promote the activity

of this enzyme is an important issue for everything having to do with biological energy.

Mitochondria from animals which are fed a diet lacking the "essential" unsaturated fatty acids are more resistant to oxidation than the mitochondria from animals fed a standard diet containing unsaturated oils, but they also have very different in vitro swelling behavior. R. M. Johnson's investigations[1] suggested that "the swelling tendency in liver mitochondria…is associated with altered respiratory and/or phosphorylating mechanisms rather than with membrane alteration." Kunkel and Williams[2] found that the very high respiratory rate of animals fed a diet lacking polyunsaturated fats was caused primarily by a great increase in the activity of cytochrome oxidase, and that adding an "essential fatty acid" strong inhibited this enzyme's activity. (Other interesting observations were that "endogenous" respiration was low in the oil-deficient animals with a high metabolic rate, and aerobic glycolysis failed to produce energy, while anaerobic glycolysis was normal. Warburg emphasized the importance of aerobic glycolysis in cancer metabolism. Anaerobic glycolysis occurs in healthy cells. Aerobic glycolysis—the kind which is typical of cancer—being energetically idle in these animals might relate to the known freedom from cancer of animals which do not receive unsaturated fats.)

Cytochrome oxidase contains both iron and copper, and the copper component is apparently responsible for the enzyme's absorption of red light. The copper's function isn't understood, but it is suspected to be involved in regulating the efficiency of respiration. A protein called metallothionein, which is induced by cortisol or heavy metals, also binds copper, and might be one of the ways in which stress and heavy metal poisoning can accelerate the process of aging and degeneration.

The similarity of the effects of cyanide and polyunsaturated fats on respiration, and on cytochrome oxidase, suggests the possibility that the "essential" fatty acids might, like cyanide, form a complex with the copper ion. Unsaturated compounds, especially unsaturated phospholipids, can form strong chelation complexes with copper.

While thyroid supplementation produces increased activity of cytochrome oxidase, the avoidance of unsaturated oils would probably, to a great extent, make thyroid supplementation unnecessary to maintain a high rate of health-supporting mitochondrial respiration.

Pregnenolone often normalizes metabolism in a way that can make thyroid supplementation unnecessary, and part of its action is probably the result of stabilizing the mitochondria. Even cholesterol (which is converted to pregnenolone in the mitochondria) seems to have a stabilizing effect, since it inhibits oxidation of unsaturated fats.

B. L. Epel,[3] discusses the evidence showing that blue light inhibits respiration by inactivating cytochrome oxidase, and says "If it is conceded that this phenomenon is universal, it is then intuitively obvious that most organisms must possess a protective or active repair mechanism since sunlight appears to be directly detrimental to few organisms."

The many studies which show that red light promotes respiration probably explain the fact that the blue light in sunlight isn't very harmful, since the sun also contains red light, which would tend to reverse the damage done by the blue light. Since red light penetrates much more deeply into animal tissues than does blue or ultraviolet radiation, larger animals would be more strongly affected by the beneficial fractions of sunlight—the internal tissues receive only red light.

The winter sickness and stress of darkness that I have talked about so much are metabolic disturbances resulting from inefficient respiration, and involve fatigue, hypoglycemia with sugar cravings, and hormone imbalances which lead to nutritional problems, such as vitamin A deficiency.

Although healthy respiration is many times more efficient than glycolysis in producing usable energy, the combined effects of getting adequate red light and using butter and coconut oil instead of unsaturated oils will cause a great increase in energy consumption. People with a significant amount of fat in their body, who have in the past eaten foods containing vegetable oils, are likely to draw unsaturated fats out of storage, with toxic effects unless vitamin E, thyroid, and coconut oil are used protectively until tissue stores of unsaturated fats are depleted. (Typically, body stores of fat take four years to completely reflect the change to a different type of dietary fat.)

Coconut oil is rich in lauric acid, which is being discussed lately as an anti-viral agent. Lauric acid inhibits glycolysis, so coconut oil will tend to prevent hypoglycemia, while providing non-glycolytic calories directly to the respiratory system.

Milk and shrimp can contribute to mitochondrial respiratory efficiency, since milk has a low iron content, and shrimp are very rich in

copper. Iron is an important catalyst in the formation of free radicals, and copper is involved in protecting against iron, as well as in the function of cytochrome oxidase. (Even before Hartroft and Porta discussed, in 1967, the free-radical promoting activity of iron which forms "age-pigment," iron was known as a carcinogen or cancer promoter.[4,5])

Anemia can cause fatigue, and iron (like arsenic) tends to stimulate the formation of red blood cells, so many people advocate iron supplements for chronic fatigue. Although the immediate effect is to deliver more blood to the tissues, providing more energy, the long-range effects are not good, especially when iron is added to a diet containing significant amounts of the unsaturated fats. When anemia is caused by something other than iron deficiency (and it usually is), it is important to find the actual cause. Thyroid deficiency, estrogen excess, various vitamin deficiencies, protein deficiency, and various other mineral deficiencies should be considered.

Cold-Inactivated Enzymes as Metabolic Controls

Physiological Chemistry and Physics, Volume 3, September, 1971

THERE is now considerable evidence[1–10] that water is ordered, though not necessarily "bound," in the presence of macromolecules and in living cells. It has been suggested by A. Szent-Gyorgyi,[8,11] G. Ling,[5] and A. S. Troshin[12] that the state of water might exert control over metabolism, cell division, muscle contraction, etc. Some of the physical changes that we would expect to occur in ordered water are increased protonic conduction, stabilization of triplet states, stabilization of hydrated electrons, altered solubilities and ionic exchange, and weakened hydrophobic bonds. Anisotropic or ordered water (such as exists in narrow capillaries)[13] can have special properties, such as lowered vapor pressure, without being bound. Polanyi's adsorption isotherm, which assumes a potential acting through space, rather than only at the surface layer, seems to be an appropriate concept for understanding these long range effects.

It has been pointed out that lowered temperature weakens hydrophobic bonds, and that this may be the cause of cold-inactivation of certain enzymes.[14] The entropic contribution to exclusion of lipoids from the water phase would be similarly diminished in the highly ordered water of cells. Thus, we would expect the cold-inactivated enzymes, e.g., pyruvate carboxylase,[15] phosphorylase,[16] and estrogen dehydrogenase,[17] to be inactivated by the ordered environment of the resting cell, and to be activated by the relatively entropic state of cells in contraction,[18] division,[11] or anaerobiosis.[19] According to Drummond,[20] phosphorylase is in fact activated during electrically stimulated muscle contraction, without activation of phosphorylase kinase or increase in cyclic 3′,5′-AMP concentration.

If entropy changes in the cell water modify the activity of these enzymes, then this behavior of the proteins can be interpreted as an important control mechanism. Phosphorylase, and probably pyruvate carboxylase, would be homeostatic, or negative feedback controls, tending to provide energy in a state of low energy charge or physical activation. However, estrogen dehydrogenase, which uses estrogen as a coenzyme, may have an opposite effect, tending to destabilize the cell. If this is the case, another hormone system would be required to override the anti-

homeostatic effect of estrogen. Progesterone, which must be present with estrogen in a precise ratio (but at a much higher concentration) for reproductive success, may be the hormone with this function. This interpretation is consistent with observations that senescent animals may have high uterine metabolic rates,† high progesterone levels,[21] and that cancer tissue often responds to steroids; that is, any nonspecific irritation or insult that increased the entropy of cell water would promote the "estrogenic" state.

It seems significant that the known cold-inactivated enzymes are in important positions for the control of metabolism. It will be interesting to look for other cold-inactivated enzymes with this mechanism in mind. Also, it might be possible to learn something about cell water by studying these enzymes in vitro, their responses to surfaces, pressure, and other physical factors.

† Unpublished observations of this laboratory.

Comparison of Progesterone and Estrogen

Long Natural Health, October 16, 2014

Natural Progesterone (Thyroid Has Similar Effects)

- Decreases bleeding, prevents PMS
- Anti-tumor, anti-aging hormone. Shrinks fibroids of breast & uterus, cystic ovaries; effective in some types of cancers, such as cervical & breast cancers & estrogen-induced tumors.
- Inhibits prolactin (which stimulates breast milk production).
- Increases body supply of oxygen, prevents hypoxia.
- Cardioprotective.
- Improves circulation, brain structure and function, including memory.
- Mimics estrogen if needed or inhibits excess estrogen.
- Helps regulate edema.
- Increases intelligence of fetus by 35 points, protects against hypoglycemia by normalizing blood sugar.
- Sedative in large doses; stops seizures, regardless of the cause.
- Protects fetus from aborting (probably by keeping blood sugar up) and helps prevent toxemia of pregnancy.
- Decreases fat storage (oxidizes fat).
- Anti-aging to skin. Makes aged, atrophied skin thicker, more regular. Increases pigment cell size and branching, but doesn't cause young healthy skin to thicken. Thus, offsets darnage of catabolic hormones and replaces deficient hormones.
- Helps prevent and reverse bone loss, even in women on ERT.
- Inhibits fibrocystic breast disease by inhibiting estrogen or balancing estrogen/progesterone ratio.

Estrogen (Synthetic or Natural; Insulin Has Similar Effects)

- Excess estrogen (and decreased thyroid function) causes PMS (edema, excess bleeding, bloating, etc.).
- Excess estrogen (and decreased thyroid hormone) linked with breast/cervical cancer, tripled rate of gallbladder disease.
- Promotes production of prolactin (like cortisone). Thus, both, acting thru pituitary (increased prolactin) may promote osteoporosis, in spite of what you have been told or sold.
- Causes oxygen deprivation (hypoxia).
- Cardiotoxic, due to causing increased calcium deposition, increased hypoxia and increased blood clotting.
- Excess inhibits memory, causes migraines.
- Increases during stress and aging in both females and males.
- Causes edema.
- Must be balanced by progesterone to prevent toxic effects of hypoxia.
- Causes hot flashes, may cause cyclic seizures (during menses) when in excess relative to progesterone.
- Excess estrogen can cause abortion of fetus at ninth week, thus is abortifacient.
- Increases fat storage.
- Causes aging of skin, makes skin thinner (skin atrophy) extending to pigment cells, decreases cell size and eliminates dendritic branches. Also true of cortisone.
- Promotes osteoporosis by causing increased soft tissue deposition of calcium.
- Promotes breast cysts even in young children who eat meat, poultry and dairy products from animals treated with a synthetic estrogen.

Concerns About Progesterone Cream and Yam Extracts

Townsend Letter for Doctors, June, 1996

I notice that on page 68 of the April issue a word was added editorially to "Preserving the tissues," a chapter from my book on the menopause, which reversed my meaning. In the 7th and 8th lines, it should say "and other factors, especially progesterone and thyroid, allowed the organism to restore itself in ways that neutralized the cortisone response," but as printed it has me saying "estrogen…called up…progesterone and thyroid, and allowed the organism to restore itself…" My original wording expressed the opposition between estrogen and the restorative factors, but your alteration has me seeming to side with those who claim therapeutic benefits for estrogen.

In spite of Dr. Gaby's good comments on the "yam scam," I notice you publish an ad for a "yam extract cream." If progesterone is "a yam extract," then so is estrogen, and so are the anabolic steroids, the glucocorticoids, and the contraceptive steroids: Does the phrase "Mexican yam root extract" or "wild yam" honestly describe the contents of the product? Obviously not, because Dioscorea, wild yam root, has been in the National Formulary for many years, as a drug in itself, used to treat "bilious colic" and as a diuretic and expectorant. In the last several years I have spoken to people in the Portland and Seattle offices of the FDA about this, as well as with people involved in the production of the "yam" creams, and it seems clear to me that the FDA is either knowingly condoning this fraudulent labeling, or actively participating in it. While they fail to enforce their laws regarding honest labeling, they have told me that I (rather than those who mislabel the products, and who have falsely used my name in their advertising) appear to be the one violating the law by writing about progesterone and related substances while having patents on them. It is clear to me that it is the scientific information which offends them, not the illegal claims and mislabelings. It is only the latter over which they have jurisdiction, and it is there that they take no action.

If the yam-substance is applied to the skin, the saponins in it might be good for cleaning the skin (it was commonly used for washing clothes, shampooing, etc.), but they will have no hormone action. If the

"menopause creams" contain estrogen, they might have a systemic effect, but the studies of topical progesterone, by Papa and Kligman, showed that progesterone had a local effect, but no detectable systemic effect. This is because of its low solubility in ordinary oils. The progesterone-vitamin E combination, which I patented, is stably dissolved so that it can be absorbed by any route—transdermal, oral, rectal, or vaginal, but I have not licensed my patent to any of the companies such as Yamcon/Phillips Nutritionals or Pro-Gest/Transitions/Professional & Technical Services, which advertise creams for the treatment of menopause. Some creams contain progesterone, some creams contain vitamin E, some contain neither. The patented progesterone-in-vitamin E products are sold only in Eugene, Oregon.

The order in which ingredients are listed on the label must be in the order of their quantity in the product. Pro-Gest's advertisement claims that "For over 17 years, physicians have recommended Pro-Gest to their menopausal patients," but I participated in the design of some of the original progesterone lotions which were sold by Professional and Technical Services (while I was "President" of that corporation), and those early formulations (I still have copies of the various brand-name labels) essentially had no effective shelf life, because of their poor formulation; the progesterone was crystallized by the time it arrived from the factory. The composition of the various Professional & Technical Services products, at least according to their labels, has changed over the years. It is incorrect to say that Pro-Gest has existed for 17 years. One formulation, for example, showed a higher content of vitamin E than of progesterone, meaning that there was sufficient vitamin E to dissolve the progesterone, and thus to infringe my patent. When I pointed this out to MacFarland, he didn't want to pay me royalties, so he obligingly changed the formulation. "Cielo 2000" another of MacFarland's previous products, moved vitamin E far down on its label, meaning that its solvent action was very limited. My samples of Pro-Gest contain massive amounts of crystals, indicating that they didn't copy my patented composition.

A friend quoted one manufacturer of a progesterone cream, as saying, when she told him of my patent, "that's easy to get around." But a truthful label will say in a simple way whether or not it is violating my patent, by indicating the relative amounts of vitamin E and progesterone.

Lab analysis shows that the products licensed under my patent contain by far the largest amount of progesterone of any product tested, but the important point is that the progesterone is dissolved in vitamin E, and is completely available biologically. Crystalline progesterone isn't available transdermally, and when it is ingested, it is quickly metabolized by the bowel and the liver, into a derivative of progesterone, which has a certain biological activity, but which is chemically and biologically distinct from progesterone.

A small amount of any herbal saponin, such as those found in the Dioscorea yams, may be harmless, but larger amounts can be lethal, by causing hemolysis, and there is also some evidence that it can cause liver damage. The people in Mexico traditionally used the yam for washing clothes and for killing fish. Russell Marker, who created the steroid industry based on the Mexican yam, took a dose of saponin while working on a project in Mexico, and was seriously poisoned. His colleague, Norman Applezweig, said the next day that he looked as if he had "been hit by a truck," because he was covered by bruises resulting from the hemolytic action of the saponins.

Criticism and the Experts

Townsend Letter for Doctors, November, 1994

The present government of the U.S. is talking about reforming the educational system and the health care system. It is clear that the insurance companies and other components of the medical establishment aren't going to be inconvenienced by the reforms. Teachers, on the other hand, are increasingly being made the scapegoats for our national decline. I want to propose that an orientation toward results, rather than procedures, is the essential reform that we need in both health care and education.

The goals of both health care and education, I think, are to maximize abilities and pleasures, minimizing disabilities and displeasures. The World Health Organization has defined health in terms of decreasing dysadaptations, and improving our adaptation to our surroundings.

As Felix Meerson (described in my monograph "Resistance of the heart") has shown, the brain is the preferred organ of adaptation, because adaptation on the level of learning has no biological costs, in the sense of limiting our structure and function. As soon as we submit to a cultural stereotype or a textbook answer, we give up our creative capacity to adapt mentally, and begin to avoid problems, questions, and mysteries, because adaptation at any level other than creative imagination is a bodily stress; the acceptance of authority commits a person to wielding any authority they have, or helplessly adapting to the authority of others. Full health requires the responsible and creative use of the mind. This is why I think it is necessary to consider the reform of health care and education together, as a single project of cultural reform.

Certain things led me into a habit of doubting the experts. For example, in high school I had a state-certified biology teacher who refused to mention the word "evolution," an American history teacher who worshipped Hitler, and a "civics" teacher who told race jokes in class. Although it wasn't their apparent intention, they were contributing something to my education. In a graduate school seminar in American literature, I mentioned the relevance of social class to the work of some writer, and the professor interrupted to tell me that "there are no classes in the United States"; I explained that I didn't mean class or caste in the legally enforced sense that India and England have them, but social-

economic classes. At that, every student in the seminar joined with the professor to make it clear that I couldn't go on with my discussion if I had to refer to the "non-existent" social classes. That same summer term, I was looking for a job at a community college, and just a few hours' drive from the great university I found myself in the midst of horrifying unimaginable squalor. My fellow students had grown up in that region, and had to know about those areas. They helped to make me aware that there are academic fetish-ideas. Later I would find that the sciences were just as susceptible to academic fetishes, but that the humanities had the advantage of a tradition that emphasizes critical judgement; while the sciences base undergraduate education heavily on textbooks, the humanities emphasize study of original materials.

Over a period of several years, I enrolled as a graduate student in seven other departments, and learned to orient myself to what I perceived as a general academic psychosis, with variations to suit the subject matter; no department, from art to zoology, was free from the crazy authoritarianism, but a small percentage of individuals in any discipline seemed able to avoid the dogmatic frenzy. Once, in the late 1960s, I tried to communicate my perception to students at the University of Oregon. I organized a course called "Interdepartmental Perspectives on the Nature of Man." We invited the most highly-thought-of professors from ten departments to lecture on "their discipline's special contribution to understanding human nature." We had professors from the sciences, social science, philosophy and religion, rhetoric, and folklore. Six weeks into the course, we had heard six professors deliver one or two-hour lectures on the central importance of Noam Chomsky's generative grammar for understanding the nature of man. After the sixth lecture, one of the students took me aside and said "You're playing a trick on us, aren't you?" Since I had emphasized that the professors should talk about their department's special contribution, I wasn't responsible for the embarrassing stereotypy of their lectures, but in fact, that student had understood my reason for organizing the class. In a later decade, "deconstructionism" might have been the specific content of the lectures, but the point would still be that the university curriculum consists largely of stylish, borderline-psychotic, garbage. (Seen from a certain viewpoint, that academic stuff seems neither trashy nor crazy, but rather elegant, noble, and relevant. You have to adopt that viewpoint to write an A

paper; you have to discard that viewpoint to do something useful. The desire for useful knowledge leads to an attitude of active criticism.)

The academic sciences and humanities are similar in their fear of responsibility for knowledge. Everyone marches in step, assigns the right textbooks, and holds the acceptable assumptions, so that they can keep their job. Ultimately (and frequently enough to keep people in line) the board of trustees exercises its power to herd the university faculty in the desired direction.

Because of my own experiences as a critical student, in 1959 or 1960 I conceived of having a college whose teachers and students were the trustees. (We called it Blake College, for William Blake.) Responsibility would be institutionalized, to some extent. To keep students from feeling that they were leaving the real world when they entered the college, I proposed that it should grant degrees based on "recognized achievement," and I specifically suggested that the BA degree should require a score above the 87th percentile on the Graduate Record Examination, since this score alone should be enough to gain admittance to any good graduate program. In fact, private universities generally recognized that a GRE score higher than that of 87% of the graduates from recognized U.S. colleges was a reasonable basis for graduate admission, but the state universities required that their applicants have degrees from "accredited institutions." (Our students all received their degrees, and their GRE scores averaged at the 95th percentile. A couple of our students had previously been ranked in the lowest 10% academically. A change of their feelings about knowledge changed their mental abilities.) The regional accrediting association told us that they would consider many factors, including the size of our endowment and whether we had a football team, and made it clear that they were a kind of mafia that wasn't sympathetic with our idea of requiring that every graduate have a high level of intellectual competence.

What this means is that competence is defined as a) enrolling in the institutions presently established by governmental authority; b) jumping through ten to forty hoops per year, for a certain number of years; the size and height of the hoops are set by the authorities in consultation with the experts; c) in certain cases, one or two flaming hoops may be required, to exalt the authority of the profession. Art Pearl, a professor of education, used to argue that students should be awarded their degrees when they enroll in college, since the degrees don't stand for any special

competence now, and the recognition of that would make people think about the actual qualifications needed for doing a job. If we compare education to the rites of initiation many cultures have, then symbolizing entry into adulthood with a college degree, earned by a feat of endurance, isn't so strange, but the ritual could be modified so that it didn't interfere with learning the things people really want to learn.

After people have proven their obedience/compliance, by years of expensive subservience, then they may be allowed to take certain licensing exams. By law, these tests are not sufficient evidence of competence, and only those who hold accredited professional degrees may take them. If people without degrees were allowed to take the licensing exams, it might be discovered that the endurance-training had a detrimental effect on the students' problem-solving abilities. Several years ago, it was discovered that students' IQs decreased with each additional year they spent in certain schools. In a study of graduate students, it was found that there was an inverse relationship between their academic standing and their distance from the mean IQ, in either direction, that is, the mean IQ is excellent academically.

If we are concerned with what people know and are able to do, then we can find ways to help them develop the knowledge and ability that they want. However if that goal is a fraud, and we really want a nation of obedient, submissive, rigid and uncritical people who don't rock any boats, then we should just worry about keeping guns and drugs out of the schools (remember the math graduate student who murdered his professor?) and otherwise keep the educational system as it is, with emphasis on form, rather than outcome.

The idea of testing for competence (with varying degrees of generality, relating to specific tasks or ability to respond to novelty) would fundamentally change our educational institutions, but its influence would extend into the workplace. Many jobs would disappear if everyone's competency improved. In medicine, people talk about payment for keeping the patient well, instead of for alleviating or curing disease, but keeping the public healthy is going to require a major social effort to keep food, water, air, homes, travel and workplaces safe. If people become aware of their potential for creative adaptation and problem solving, the whole direction of the economy must change, because status and style-dependent consumption derive their importance from the absence of intrinsic interest in many of our activities.

Active criticism is an old idea that is close to "imaginative science." B. G. Niebuhr is considered to have founded German historiography with his concept of criticizing the source documents. Goethe used the phrase "tatige skepsis" (active doubt, constructive criticism) to describe Neibuhr's method. William Blake emphasized that criticism and imagination must be combined to correct error; doubt by itself is futile, imagination is vulnerable without organized and active criticism. More recently, Salvador Dali's concept of "critical paranoia" advocated the same intelligent use of the brain, to discover what is true, important, and interesting in ambiguous situations. Meerson, the investigator of stress physiology, speaks of adaptive culture as the first level of protection against harmful conditions.

For about 50 years, the concept "psychosomatic" has been trivialized to mean "it's just imaginary." But now, the studies of the physiology of helplessness show that a seemingly small difference in experience and attitude can cause a very great difference in the ability to mobilize biological energy and various aspects of immunity, such as Natural Killer cell activity. There is now general agreement on the distinction between the demobilized state of helplessness and the state of active adaptation. If everyone could be "vaccinated" against helplessness, there would be a general improvement in health and ability to learn. But irrational institutions keep making helpless people. A culture which promoted a responsible, creative use of critical intelligence would minimize the experience of helplessness; and at the same time it would shift our adaptive habits upward, toward seeking reasonable imaginative solutions to problems that now are often perceived as stresses and threats.

After my experience at Blake College, in which the essence of the institution was to support the inclination of students and teachers toward being responsible for knowledge, I found that it was often possible to reinterpret institutional rules to create a similar temporary environment within the existing conventional universities.

The greatest impediment to doing this is probably the fear of unemployment; subscribing to the current academic idiocy, or the current cliche of the marketplace, is felt to be necessary to fit in. In questions of health and education our culture is at a critical point. Things could be reinstitutionalized to give all power to the drug, insurance and communication industries, or they could begin to be de-institutionalized to expand the scope for intelligent individual activity.

Art Pearl's suggestion that students be automatically granted degrees can be seen as the student's equivalent of tenure. If teachers were much more secure about their jobs, there wouldn't be so much pressure to conform. There are foolish and wicked teachers, and good and wise teachers. If students know there are objective standards of achievement, they won't be under the teachers' power; teachers will be challenged by the needs and curiosities of the students. Students will necessarily become conscious of the need to examine and question the source of information. Little kids naturally have that inclination, which is the inclination of good scientists and artists.

The Japanese have relatively high levels of achievement in education. They also invented crawl-in hotel "rooms," stuffers to pack people into subways, and snap-on apartments. Their achievement comes at the price of exhaustion, misery, and diseases of stress. They represent one of our potential futures. The other potential future takes into account our health and happiness, and defines health as having the capacity for creative mental adaptation.

Critiquing "Dr. McDaniel Responds" Letter

Townsend Letter for Doctors, August/September, 1996

PEOPLE have expressed concern to me about statements in the letter (June, 1996) from H. Reg McDaniel, Director of the Fisher Institute for Medical Research. Although it is headed "Dr. McDaniel Responds," the letter isn't responsive to Kenneth Sancier's questions, and even seems to further blur the "identity" issue that Sancier asked about. The editor describes McDaniel as a consultant for the company that markets "dioscorea." I don't know if that is accurate. Dozens, maybe hundreds, of people have asked me about a chart used in marketing Emprise products that indicates diosgenin is a precursor of DHEA. Although I can't imagine what enzymes might achieve that conversion, no one seems to want to say whether their products contain diosgenin or DHEA or yam tissue. If they contain yam tissue, then they should be discussing the issue of toxicity.

I don't doubt McDaniel's claim that the statements he makes "reflect the consensus of a research pharmacologist, biochemist, molecular biologist, gastroenterologist and gastrointestinal physiologist, as well as physicians who interpret scientific data…" While the editors of *JAMA* make similar claims about the authoritative nature of their publication, I noticed a completely idiotic statement about yams and steroids in that journal, indicating that the yams used by the steroid industry were the same as edible yams. (There are about 600 types of steroid-rich yam; a typical one looks like Bigfoot, weighs as much as 90 pounds, and is poisonous.)

McDaniel's group of specialists were asked to evaluate the set of articles cited in his letter. It would seem that neither McDaniel nor his professionals bothered to read the articles. Although none of McDaniels' sentences stands up to close scrutiny, let me comment on half of one of his sentences: [animals] "…were administered diosgenin and it was converted by the adrenals to pregnenolone and then to estrogen, (3) oral diosgenin reversed experimental diabetes, (4) oral diosgenin lowered blood cholesterol levels, (5) diosgenin has also shown the capacity to induce megakaryocytic differentiation of bone marrow stem cells in tissue culture; a demonstration of hormonal regulatory influence at the cellular level expressed free of other sources of endocrine influence…"

Far from saying that diosgenin is converted by the adrenals to pregnenolone and estrogen, Rao, et al., say it has not been ascertained whether it acts directly or by being metabolized. Their evidence argues against that, by "excluding any possibility of diosgenin having progesterone-like activity in mouse," since any pregnenolone produced would be far more likely to produce progesterone-like effects than estrogenic effects. A. Lipshutz's work made that clear.

Although I am not familiar with dioscoretine, and haven't read the paper by M. M. Iwu, et al., their abstract strongly suggests that it has nothing to do with diosgenin, because their hypoglycemic substance has an LD50 in mice of 0.58 g/kg, and diosgenin isn't likely to be that toxic. The paper by Iwu, et al., wasn't about "reversing diabetes," but only about the observation that dioscoretine lowered blood sugar after four hours in rabbits. Thousands of other seriously toxic substances can cause a sudden decrease in blood sugar.

McDaniel indicates that Malinow, et al., studied the effects of oral diosgenin on cholesterol, but, as their title says, they were examining digitonin, a toxin from a different family of plants. Since McDaniel brought up the subject by citing this digitonin study, I should mention that one of the effects seen by other researchers, with Dioscorea-derived compounds, is chronotropic heart stimulation, suggesting a parallel to digitalis.

Beneytout, et al., describe the HEL cells as a human erythroleukemia cell line, which isn't the same as McDaniel's description of them as "stem cells"; and they compare the effect of diosgenin to that of phorbol myristate acetate treatment, and say nothing that could be construed as "a demonstration of hormonal regulatory influence at the cellular level expressed free of other sources of endocrine influence." Phorbol myristate esters are recognized as potent co-carcinogens. Both diosgenin and PMA caused an increase in the number of cells containing 4 or more nuclei. Diosgenin, we might conclude, is as effective as PMA in promoting abnormal development in cancer cells. This would suggest that diosgenin is something to be avoided.

If McDaniels gets paid for mentioning DHEA, pregnenolone, diosgenin, and dioscorea on the same page, he has done his job. But the *Townsend Letter*'s important forum for uncensored dialogue is abused when someone uses it repeatedly for evasive verbiage and misstatement of fact.

Darkness, Water, Osteoporosis

Townsend Letter for Doctors, April, 1985

AROUND 1973, there was an interesting observation, in which eyes that had been burned by ultraviolet rays were treated with red or infra-red light, and the pain was relieved. Since I had been interested in solvated electrons, I wondered if this medical observation might involve a mechanism similar to the "bleaching" of trapped electrons in crystals or glass which has been colored by exposure to x-rays or gamma rays. Szent-Gyorgyi used to demonstrate that structured materials, e.g., ice, can stabilize excited states of electrons. He was curious about the existence of pigments inside organism, and suggested that they related to metabolic electrons, since he assumed that external light didn't reach these tissues.

In December, I drove in sunny weather all the way to Houston, and thought about light. Having read that the leaves of deciduous trees go into a negative protein balance (work by K. Thimann, U.C. Santa Cruz) as they age in the short days of autumn, I realized that the mechanism of aging that I have discussed in other newsletters could be general for all living things. Knowing that plants have "photo-respiration," that is, the respiratory production of usable energy during stimulation by light, I wondered if animals might have something similar, accounting for winter sickness, dark-stress, and aging itself.

Knowing that photosynthesis uses orange-red light (though other plant processes are stimulated by other colors), I wondered if that frequency also stimulated photo-respiration. Anyone who has held their hand over a bright light knows that red light does penetrate tissue. Pineal researchers planted a photoelectric cell in a sheep's brain, near the pineal gland, to see whether significant amounts of light reached that organ directly, and the device clearly indicated when the animal moved from shade to sunlight. So, when I got home I was thinking about how to design an experiment to test the direct effect of red light on tissue respiration, especially in the brain.

I had been home for a couple of days when a journal arrived in the mail, describing exactly the sort of experiment I needed to test the idea. Rats had a bright red laser beam shined on their heads for 15 minutes, and then the respiratory enzymes of the Krebs cycle was studied. The changes were consistent with enhanced respiration.[1] (The red laser has

been used for more than ten years to promote healing—references will be provided on request.)

So my present thought is that darkness does in some way "poison" respiration, and that light enhances it, possibly by the indirect mechanism of disposing of electrons that have leaked out of the usable-energy pathway.

When respiration is blocked, tissue takes up water. A simple illustration of this is the cornea—when contact lenses were very impermeable to oxygen, they caused severe corneal swelling. I think estrogen works by the same mechanism (and this explains why so many toxic substances are "estrogenic"). There was a doctrine that cells can move water only by moving sodium, so medical textbooks say that estrogen causes sodium retention; but it occurred to someone to actually measure the effects of estrogen on sodium and water, and they found that estrogen causes the fluids to become hypotonic, with a lower than normal sodium concentration.

Estrogen (like darkness and stress) promotes prolactin secretion. A previous newsletter discussed the experiments in which sodium suppressed prolactin secretion, while taking water without sodium stimulated it. So it seems likely that hypotonic (or sodium deficient) tissue fluids might be a common factor in the various situations which increase prolactin secretion.

In the salmon which swim up the Columbia river to spawn, the fresh water, which is very sodium deficient compared to the ocean, does stimulate the secretion of prolactin, and the prolactin is involved in their adaptation to the fresh water. The adaptation is very costly, though, because these fish undergo very rapid aging. Their bones are transformed in ways very similar to the bones of other animals in extreme old age; for example, the back humps and the jaw juts forward. (Since the fish vertebrae don't bear weight as those of a biped do, we shouldn't attribute the bending of the human spine in old age to "compression.")

Some recent studies have investigated prolactin's involvement in calcium disposition, and its contribution to osteoporosis. (Growth hormone is closely associated with prolactin,[2] and I mentioned in *Nutrition for Women* that there was some basis for thinking that estrogen might make osteoporosis worse, acting through the growth hormone. The editor of the *Yearbook of Endocrinology* (1984, 273) says "Consider, if

hyperprolactinemia leads to osteoporosis, and the administration of estrogens to postmenopausal women leads to hyperprolactinemia…")

Since it is established that excess prolactin does contribute to osteoporosis in humans, it seems reasonable to suppose that the dramatic increase in prolactin secretion when these animals enter fresh water would be the cause for the equally dramatic skeletal changes in the fish.

It is already known that excess calcium damages respiration and that calcium is associated with structural disruption of the mitochondria, and that tissues tend to calcify in aging. Inside cells, calcification begins in the mitochondria; outside cells, for example in blood vessel walls, the "ground substance" (a fine-textured component of connective tissue) can become calcified.

Hypotonic fluids are disruptive to life processes and structures. Even tissues which are not very cellular, such as cornea, joint cartilage, and the various "basement membranes" (which are rich in ground substance) can be damaged.

I suspect that we—fish and humans—have a simple way to protect ourselves from "hypotonicity," that is, from a deficiency of salts in our fluids. (There have been various observations in which one salt can substitute for another, at least to the extent of preventing an immediate disaster.) We carry with us a huge reservoir of minerals, our skeleton. In osmotic stress, it is better to lose bone material (and teeth) than to experience hypotonic disruption.

Undoubtedly the liberated calcium participates in adaptation in ways besides preventing swelling of the connective tissues, but I plan to examine the metabolic effects of calcium in future newsletters. (The bones also provide a large reservoir of sodium.)

Both prolactin and cortisone are secreted during stress (and in darkness), and both mobilize calcium. If calcium is so harmful to our energy producing system, why do the stress hormones dose us with it? I think this is largely explained by the generality of hypotonicity in stress, and by the convenience of the skeleton as a mineral reservoir. Selye illuminated estrogen by comparing it with the initial shock phase of the stress reaction (before adaptation begins), but the value of the comparison probably goes the other way, too. The essential element in stress is the inadequacy of energy to meet a challenge, and when energy is insufficient, water is taken up. (And some water is produced in the cell when oxygen is

electronically reduced; this "respiration" is not necessarily involved in energy production—even "age pigment" can convert oxygen into water.)

Selye found that various stresses caused connective tissue disease, such as scleroderma and arthritis. He didn't explain the mechanism. I think it is significant that women are much more susceptible to many connective tissue diseases than are men. For example, a recent Arthritis Foundation advertisement says that women are twice as likely as men to suffer from arthritis. Fibrositis, myositis, etc., are common in women. (I think the studies of adhesions being prevented by progesterone provide a good model for understanding connective tissue disease, and allergies or "auto-immune" diseases.[3]) When cartilage is soaked in distilled water (or hypotonic body fluids) it swells with tremendous pressure. The microscopic mesh of this connective tissue is rich in negatively ionized groups, which attract neutralizing positive ions, such as potassium and sodium. As the neutralizing ions are leached away, the negative ions repel each other, causing swelling and attracting more water. As positively charged calcium ions are made available from the bones, the swelling is blocked. Continued for a long time, this seems likely to lead to conditions such as arteriosclerosis and scleroderma.

Structural disruption of the mitochondria, as well as uncoupling phosphorylation from respiration, can be caused by cortisone. So it is interesting to see seasonal changes in the structure of the mitochondria, which are consistent with the ideas I have been talking about, that winter (and light deficiency in general) is what ages and kills us.[†]

Winter stress, elevating cortisone, could also be the reason for the non-adaptive depression of thyroid function in the winter. Many people have noticed an association between stress and periodontal disease. Gum disease is common in hypothyroidism, and bone loss is an important part of the periodontal disease. This same endocrine pattern, and not "postmenopausal estrogen deficiency," is the most likely explanation for osteoporosis in aging women.

When I was working on my hamster thesis, about 1971, I noticed an article which reported that aging women's urine revealed an increased ratio of estrogen to the 17-keto steroids. I think it was that article that

[†] A couple of other things to notice in regard to stress and season: in men, the sperm count, and in both sexes, the visibility of veins on the backs of hands when they are held at waist level.

started me thinking of aging generally in terms of a deficiency of anti-estrogens, including things such as DHEA.

DHEA has been studied in relation to osteoporosis. J. Hollo, et al.[4] reported that "Administration of norandrosterone decanoate or dehydroepiandrosterone to patients with menopausal osteoporosis resulted in normalization of the postload hypercalcemia. Calcium tolerance of menopausal patients without osteoporosis was not affected by dehydroepiandrosterone."

S. Brody, et al.[5] found significant positive correlations "between basal levels of DHAS and the DHA response to ACTH respectively, and trabecular bone mineral content of the distal forearm."

There was a study of prolonged DHEA treatment on rat bones, which I haven't found.[6]

I think rational therapy for osteoporosis would include thyroid, vitamin A, bright light, and either pregnenolone or a mixture of progesterone and DHEA, with a diet rich in protein and all the salts: calcium, magnesium, sodium, and potassium. A bias toward magnesium, rather than calcium, would protect against many conditions that occur in aging and stress.

Diagnosing Porphyria for Labor and Industries Claims

Townsend Letter for Doctors, April, 1996

POLYCYTHEMIA, scleroderma, and porphyria have several elements in common, but I have never seen a discussion of this. Although I have written about them before, my articles on these subjects haven't been widely published. When I saw all of these topics mentioned on the same page of the *Townsend Letter* (February/March 1996, page 98), it seemed that I should point out some of the features that make these a sort of family of disorders.

These are disorders of tissue respiration and energy production. Oxygen, estrogen, and iron have important roles in all of them. Men are more likely to have polycythemia, women are more likely to have scleroderma and some types of porphyria.

The Washington State Department of Labor and Industries' review of porphyria is representative of a bureaucratic approach to a disease in its exclusion of all of the publications that offer an opportunity to understand its mechanism in a general way; I think it is setting the stage for a pro-industry/anti-worker policy, in drawing its distinction between problems "triggered by" exogenous chemicals, and those "potentially caused by an exogenous chemical exposure." Scientifically, this sort of categorization is meaningless. I think it is reasonable to interpret any increase in porphyrin metabolism as possible evidence of work-related damage, which compromises the worker's adaptive capacity in many ways.

The document at one point approaches a recognition of the silliness of their approach: "It can be argued semantically that this was not a true 'porphyria,' because of the absence of hereditary enzyme deficiency; however, there is little question that this acquired 'porphyria-like' condition was highly morbid and also clinically indistinguishable from the inherited form of porphyria cutanea tarda."

Until the doctrine of significant genetic causation is subjected to the requirement of being obtained in "a rigorously designed, blinded and appropriately controlled manner," it would have to be considered "speculative and unestablished," if this document were coherent. (It appears that its authors drew their gun intending to cripple a branch of

alternative medicine, and shot their argument in the head.) The document's emphasis on defining the disease in terms of genetic deficiency gives the enterprise an overwhelmingly anecdotal quality, at best. Let us see the rigorous evidence on which the categorization is based.

The document bases its whole presentation on the presumed reality of "hereditary deficiency" of enzymes, and—probably for a reason—ignores the evidence for an enzyme excess, which can be so easily induced chemically or hormonally. Early steps in the porphyrin synthetic pathway are influenced by the availability of precursor substances and by the concentration of heme, and are extremely susceptible to environmental influences. The issue of the role of genes in the balance and organization of a complex enzyme system is so tenuous that the citizens of Washington should look into the state's manner of choosing its experts.

There is a long history of investigating the interactions of porphyria metabolism with estrogen,[1] with cancer,[2] with diet, and with excess iron. Estrogens are known to cause porphyria,[3] and to exacerbate the symptoms and biochemical disturbances in people with subclinical porphyria. Sometimes symptoms occur premenstrually, during the time of increased estrogen production—the term "ovulocyclic porphyria" has been in use for a long time. Puberty therefore increases the susceptibility to symptomatic episodes.

Porphyria synthesis begins at an important cross-over point of protein and carbohydrate metabolism. Succinyl CoA and amino levulinic acid can enter the Krebs cycle or the porphyria pathway. Protein catabolism feeds into these pathways. Increased protein catabolism or blockage of oxidative consumption of Krebs cycle fuel—for example by poisoning—makes these precursors available to enter the porphyrin pathway. Stress-induced oxidation of heme can eliminate feedback control, but the specific outcome can be modified in many ways.

Many serious long-range consequences of excess heme/porphyrin production and metabolism are currently being investigated, suggesting that a criterion of "twice the upper limit of normal" excretion, for recognizing that a problem exists, could allow far more serious problems to develop over time, that on the surface might seem unrelated to porphyria. In some cases of porphyria cutanea tarda, scleroderma-like hardening of skin occurs, but the ramifications of disturbed heme metabolism, resulting from exogenous factors, are far-reaching. For example, G.Y. Kennedy,

at the Cancer Research Laboratory, University of Sheffield, observed that a porphyrin shortened the time required to induce tumors, and porphyrin derivatives have been proposed to be "cancer hormones." The carbon monoxide produced in the breakdown of heme inhibits many enzymes.

The synthesis of heme/porphyrin, and the production of red blood cells, are stimulated by a lack of oxygen, or by toxins such as arsenic and iron, which cause oxidative stress. Emphysema, high elevation, sluggish circulation, and nocturnal breathing problems can cause enough oxygen deficiency to stimulate the formation of new red blood cells. Newborn babies often have polycythemia, as a result of limited prenatal oxygen supply.

At a certain point, the continued production of red blood cells can make the blood so viscous that this viscosity impairs circulation through capillaries, and creates a vicious circle, stimulating the formation of more red blood cells. Men are more likely than women to have polycythemia rubra vera, possibly because testosterone is anabolic to the bone marrow, and estrogen tends to slow blood cell formation (females of all species are relatively "anemic," compared to males, partly because their blood is more dilute), but I think the greater ability of men's marrow to respond proliferatively to hypoxia is influenced by many factors, including different nutritional requirements. (Estrogen tends to cause certain vitamin deficiencies and fluid retention.) Estrogen also significantly lowers body temperature, while testosterone tends to raise it, and the temperature of the bones is a powerful factor in forming new blood cells. But this isn't to suggest that the patient could benefit from increased estrogen, because estrogen consistently lowers the availability of oxygen.

Excess estrogen reduces the blood's oxygenation, for example by producing a barrier to oxygen diffusion in the lung. Hypothyroidism (which is causally related to an excess of estrogen) is known to predispose to emphysema, and treatment with thyroid hormone has often cured polycythemia vera, presumably by improving respiratory efficiency. Progesterone, which is known to stimulate the brain's respiratory control system, has also been used successfully to treat polycythemia, and in animal studies it corrects experimentally induced emphysema. (These treatments for polycythemia vera were mentioned about 30 years ago in *JAMA*, I think, though I don't mention that to give the observations credibility, just to show how generally distributed the information has

been). In Colorado, where the incidence of polycythemia is high, it was found that teaching men to get in the habit of breathing more deeply could solve the problem.

Although there has been a medical faction that liked to compare polycythemia with leukemia, to justify treatment with radiation or cytotoxic/carcinogenic chemotherapy (and following the treatment, the patients did get leukemia, confirming the doctors' belief in the connection between the two diseases), simply removing some blood and replacing it with fluid to bring the volume of red cells down to 45 % to 50 % improves exercise performance in polycythemia patients with chronic bronchitis, emphysema, overinflated lungs and hypoxia,[4] H.P. Ward, et al.[5] found that in some patients, lying down or sleeping could cause enough oxygen deficiency to increase red blood cell formation.

Increased viscosity of blood, and increased levels of adrenalin produced in response to hypoxia, cause increased risk of excessive blood clotting and thrombosis.

In my experience, clinical emphysema responds very well to pregnenolone, and for men, this has advantages over both progesterone and thyroid.

Impaired lung function is very common in scleroderma, even when there seems to be no evidence of lung involvement.[6]

Metal poisoning is often mentioned as a cause of both porphyria and scleroderma. It was probably this medical association that caused Hans Selye to create the animal model, in which the injection of iron contributed to the development of scleroderma.[7,8] Injected iron damages the liver,[9] and practically any kind of liver damage leads to estrogen excess and a chronic stress-like adaptive response.

Scleroderma used to be described as one of the "collagen diseases," because similar changes in blood vessels and connective tissues were seen in systemic lupus erythematosus, rheumatoid arthritis, polyarteritis, drug hypersensitivity, etc.[10]

Scleroderma (similar to several other "autoimmune" diseases) is much more common in women than in men, and animal models for several autoimmune diseases can be produced with estrogen treatment. Scleroderma often begins with edema of the extremities, Raynaud's phenomenon, and muscle weakness or "polymyositis," which are commonly seen in hypothyroidism/hyperestrogenism.

It is generally agreed that collagen is overproduced in scleroderma, and there is evidence of increased mucopolysaccharides in the skin.[11] This is reminiscent of hypothyroid myxedema; it has been suggested that mucopolysaccharides can act as a matrix for calcification.[12] Estrogen stimulates the formation of collagen, and increases its age-like properties, and progesterone opposes some of these pro-aging effects on connective tissues. Mere lack of oxygen stimulates collagen formation, and the opposing effects of estrogen and progesterone on tissue oxygenation can account for many of the tissue changes they produce.

Oxygen deprivation causes tissues to retain calcium (and iron), as does estrogen in many cases, being similar to aging in promoting cellular uptake of calcium. Since the porphyrins strongly bind metals, it has been suggested that they may have a role in mediating the deposition of metals in stressed tissues. Paroxysmal vasospasm occurs in about 90 % of scleroderma patients, and estrogen and adrenalin are known to synergize in producing vascular spasm; hypothyroidism normally involves elevations of both estrogen and adrenalin.

I have known women who developed scleroderma after beginning the use of estrogen, and who are reluctant to stop, because they had been told that estrogen would protect them from osteoporosis and heart disease. Men who have had a diagnosis of scleroderma have told me that with the use of thyroid and magnesium supplements, Epsom salts baths, and topical progesterone and vitamin E, their symptoms regressed.

Polymyositis sometimes leads to calcification, and this would be expected if the problem is related to mitochondrial respiration, as is now generally thought to be the case; thyroid and magnesium are often the factors needed to normalize mitochondria and prevent calcification.

Tumoral calcinosis is sometimes treated as a variant of scleroderma, but it is very different, and tends to be localized, without internal complications. I think many people get minor bony excrescences (bone spurs, osteophytes, exostoses, hyperostoses) during puberty, or at other times of hormone imbalance, which often disappear spontaneously, but this probably represents the same basic process, and would have very little to do with the severe oxygen deficiency states in which collagen synthesis is overstimulated. Growth hormone and prolactin imbalances have been suspected to have a role in some of these growths. (Both of these pituitary hormones are elevated by estrogen, and hypothyroidism

is often the cause.) Progesterone, thyroid, bromocriptine, and other things are available to normalize the pituitary, when that is responsible.

A weakened ability to oxidatively produce energy can lead to the maladaptive over-production of collagen, porphyrins, and red blood cells. Considered together, I think the mechanisms involved in these diseases argue for the importance of the nutritional-environmental approach to health care. The medical/bureaucratic preference for a "genetic" rationale for disease has overtones of "eugenics." When the state gets involved in genetics, eugenics, or medicine, they had better keep their own scientific standards at least as high as those they demand of the people they disagree with.

Education Against Knowledge

Townsend Letter for Doctors, December, 1990

> "There has to be a way to measure the quality and efficiency of a clinic just as there are ways to measure the same characteristics in a baseball pitcher."
>
> — Former Surg. Gen. C. E. Koop

YEARS ago, I was told by our state Superintendent of Public Instruction that "what students know has nothing to do with education." Since then I have occasionally wondered how many other people with responsibility for education have such a clear awareness of their social function. Many teachers and professors, who emphatically claim that education has something to do with knowledge, nevertheless will claim that there is no objective way to measure knowledge. Many of these teachers will base their students' grades on examinations, yet it is rare for a school or college to allow a student to take those same exams for full credit without enrolling in the course. Several professions require an examination to qualify for a license to practice, yet will administer the test only to people who have the appropriate degrees, as if the examination (which excludes a fair number of degree-holding applicants) were unable to exclude those with inadequate knowledge.

The National Endowment for the Humanities has done another study, this time showing that U.S. college seniors generally don't know very much. In their earlier study, they found that the average young person in the U.S. knew less about the world than people of the same age in Mexico, Italy, and all the other nations studied. I suppose this country spends at least 50 times as much on "education" as Mexico does. Dr. Koop has pointed out that "health care" in the U.S. is deteriorating, at the same time that its cost is increasing. Just as he proposes that medicine should adopt the serious and objective concern for performance that exists in baseball, I would propose the same for education.

The fear of objectivity in education and in the professions has to do with power. When a professor has secret criteria, his judgment can't be challenged. If his assumptions are unfounded, a student could

embarrass him by examining them. But, in a system which requires an accumulation of course-credits, good students quickly learn what is expected of them, and after a few years of learning not to question the assumptions of their "discipline," they are ready to become like their teacher.

Listening to an expert talk about a subject is often a good way to learn, but having your understanding judged by that same expert is very likely to inhibit a spirit of objective inquiry. Separating evaluation from instruction can make a tremendous difference in education. Students and teachers can disagree, and still have a sense of working together. Venerable dogmas and stylish trends can remain in the curriculum, but their mystique is likely to evaporate. Even textbooks are likely to change, because they are now designed to serve the teachers (who select them) rather than the students who use them. Whether the subject is music, or math, or language, or physics, textbooks are likely to be instruments for maintaining a mystique, rather than for directly communicating an understanding of the subject. Vague or fragmentary definitions of terms and symbols often make the subject seem more mysterious than it is.

I have seen teachers present in a day the material that they would normally teach in a semester or two, and it seemed that their students grasped the subject as a whole more clearly than the conventional students who attended dozens of lectures. This was in the early 1960s, at Blake College. This school has been described as a prototype for the experimental college movement of the 1960s, but my intention in creating it was to demonstrate what can happen when students are not required to conform to the cultishly departmentalized attitudes toward knowledge which dominate most schools and universities. Simply by letting the students know that professionalism was not sacred, they were allowed to see how easy it is to master the information which is normally so laboriously and pompously inculcated.

In a miniature way, my composition class at Montana State (1965–66) demonstrated the same process. The department "required" each instructor of freshman composition to grade according to department rules, subtracting so many points for misuse of a comma, or for using the wrong part of speech, or misspelling, etc., with the result that 50 % of the students failed the course. A few weeks into winter quarter, I decided that the procedure was just too pointless and degrading, for both students and teachers, and I told my classes that I was going to ignore their grammar

and spelling and punctuation when I decided on grades for their papers (though I still pointed out the conventional errors), but that I was going to grade on the content of what they said. If they communicated something of interest, they would get a good grade, but if they kept writing on the level of a grade-school child (which they did in an effort to keep the mechanics of writing simple, hoping to minimize errors) I would give them an F. They immediately started to write more interestingly and more complexly, and the errors in grammar dropped sharply, so that nearly all of them were passing even by the stupid departmental requirements. That spring, the university solicited grant applications for research projects to improve education, so I submitted a description of my class, with before-and-after examples of the student's writing, to demonstrate the dramatic improvement. Only one other person, out of the 40 teachers in the department, would talk about the idea of writing for content; I'm sure that the department chairman didn't forward my proposal to the committee that had solicited research proposals, since so many of the old-timers in the department were committed to the idea that the department's "standards" would be lowered if they didn't fail half of the freshmen. (Incidentally, the courses were called "Communication 121," etc., so I argued that it was proper to grade the students on the basis of communication, rather than form.) Since then, I have heard many people justify various "educational" ordeals, by saying "that would be like a child trying to learn to speak before learning the alphabet," or something to that effect. Their examples usually make exactly the point they oppose; for example, it would be a seriously distorted child who learned the alphabet before learning to speak. And much of our educational system, at various levels, is devoted to just that kind of distortion.

Unless the dogmatic power of "the authorities" is replaced by some objective standards of knowledge and skill, public knowledge will continue to deteriorate. Our interactions with the environment, with each other, and with other nations will continue to deteriorate. Public health and the standard of living will deteriorate, unless knowledge is treated with the same seriousness as the skill of athletes.

Education, Energy, and Ideology

Energy and Character, Volume 4, Number 2, 1973

GIVING students a place to be free, to find a self, to do some things they couldn't comfortably do elsewhere, is a useful thing that can be done by a free college, as well as by free schools for younger children. This function has (particularly in the early 1960s in America) been part of the process of creating a new culture "inside" the old one. The school had an insulating function, as well as a creative function.

But as the idea of "free colleges" became popular, around 1966, students started arriving at "free schools," such as Blake College, with preconceptions that had been shaped by filtering through mass media. Passivity, conforming to a certain role, was an alienated attitude that free schools had helped people overcome, but now it was an increasingly explicit expectation of new students. Instead of using freedom to overcome passivity, they identified passivity with freedom, and defended it. The role of "passive counter-culture rebel" was a fine capitalist invention. (Richard Alpert/Baba Ram Dass can be seen as the vanguard of the ruling class with his empty mysticism of passivity.)

In this setting, the creative function of the free colleges became increasingly important, but, as far as I know, Blake College is the only one that has consistently tried to make this clear. Over ten years ago, when the foundations that had denied support to us began funding parodies of our program in very conservative universities, we felt that the forms of experimental education were being disarmed and corrupted, so that exploitation could pass for innovation.

As a result, we have tried to emphasize that the beliefs that justify the form of the free college should also serve as guides in the integration and creation of knowledge. Just as Marx's perception of man's potential guided his understanding of alienation and exploitation and social development, it is a revolutionary body of knowledge that originally supported ideas of educational reform. We feel that our function is to contribute new knowledge and coherence to it, while disseminating it and using it in humane ways and as a tool of resistance against the alienated-alienating culture of the exploitive society.

In organization, we have de-emphasized the recruitment of students to support teachers, and have become a small group of self-supporting

collaborators, accepting students only on terms that will not contribute to further alienation.

Respect for the complexity and potentiality of matter is the foundation for this revolutionary body of knowledge. Use of the body as an instrument of discovery is an important part of our phenomenological method. Radical empiricism and dialectical materialism are among our commitments.

What Heraclitus, Blake, and Marx had in common was an intense honesty of method, and a perception of the tremendous potential of people who devote themselves to that kind of knowing. Many others including scientists such as W. F. Koch, M. Polanyi, and W. Reich, have extended this self-development into the natural world. Besides helping to expand our perceptions and knowledge, their great contribution has been to demonstrate a way of knowing and discovering that is simply human (and animal), but which contradicts all formalized doctrines of scientific method.

As I understand it, intuition is guided into even the subtlest and most complex aspects of the material world by the fact that subtle and complex aspects of matter and energy constitute consciousness, and that related and simple tendencies exist in both knower and known. Blake and Reich and S. Dali suggest that it is the erotic impulse that guides intuition, and prevents "paranoia" from being "uncritical" (Dali's terms). The materialist tradition in its richest form recognizes desire and the directionality of time; alienated or mechanistic materialism makes the absurd assumption of randomness whenever possible, as a complement to their ruling atomistic and deductive logic.

When consciousness is seen as a material and energetic model or image of the world, rather than as an alienated set of rules and symbols, it is more likely to function in a productive, unalienated way.

For us, science is important as an amplification of the human—both as perception and as function. The fact that stimulation can cause an animal's brain to grow—even in maturity—and can lead to inherited larger brains, suggests the significance of cultural evolution to the organism.

Perception is extended, just on the psychological level, by the discovery of new rules of interaction—what was random, now can be seen as ordered. This is vaguely analogous to the function of myth, except that this is both perceptual and interpretive, while myth is mainly just interpretive. A higher energy state of the brain allows awareness of a

broader span of the present, so that patterns which exist only or partly as a development through time can be perceived and used. Old theories of discovery could do no better than proposing a mysterious kind of luck in hypothesizing to account for the scientific success of some people. Mere intensity of animal perception is the whole trick. The difference from ordinary animal perception is its ability to dream new integrations when there is slight discordance of elements—i.e., it is more fluid, and able to be introverted.

An example of trying to amplify a function is the project of trying to find why some populations can fix enough breathed nitrogen to meet their protein needs, while in many populations protein starvation is very real. If a deficiency of vitamins or minerals is responsible, this would be an easy way of amplifying our "normal" function of fixing atmospheric nitrogen in our bodies for use in protein synthesis.

The emphasis put on the work function by Marx and Reich, the idea that real history begins when we can start realizing and creating ourselves through our work, combines an affirmation of time with a recognition of organismic energy.

Another perspective on the same idea is this: dreams affirm and shape life. The morphogenetic field of biological energy, which shapes growth and renewal, is known directly as consciousness; the dream cycle is also a voltage and resistance cycle, for example. G. A. Sacher has observed that brain mass correlates very well with longevity, and others have observed that the dream-activating function corresponds to brain size. Babies apparently dream very often and intensely. We feel that infancy is the direction of our evolution, biologically, and that the cultural stereotype of a child as one who doesn't work has to be overcome—kids are naturally high-generality problem solvers, wanting to contribute immediately to the world that has been reserved for adults.

Our invitation to others—students or teachers—is to come and play and dream with us, in our work of evolving ourselves and the culture. We are appropriating cultural achievements for ourselves, making them new and extending them, and looking for as many other peculiar cultural centers as we can find, because unique perspectives provide the richness for growing generality. We want our physics and our psychology and technology to incorporate the vision of the Mexican mountain villager and the Nepalese brahmin, because every village culture represents thousands of years of experience that will enrich our own village perspective,

"western civilization." The desirable high-generality integration will be many-levelled and rich, unlike most previous cultural syntheses.

European culture is flat and abstract; Mexican culture is many-levelled, but undergeneralized; China is the closest to our ideal of rich generality, especially its Taoist tradition with a dialectical awareness and emphasis on body, energy, and life.

The institution, or the person, that performs the "higher education" functions of discovery, communication, and criticism should have a vision of matter, organism, and society that serves as a guide to growth and liberation. Blake's statement, that unorganized innocence is an impossibility, should remind us that comprehensive understanding is necessary just for defense.

The dialectical idea of "criticism" has internal application, as well as being the proper interface with the static culture. The general way I use the concept is illustrated by some examples: Russian psychologists trained children to use the hand they weren't accustomed to, and found that their "characters" were improved, nervous heart conditions disappeared, etc. Alexandro Jodorowski used a theatrical form in which the actors present their "weaknesses" in dramatic form, and experience loss of some of their rigidities of character. Through his studies as a mime, Jodorowski discovered the neurological principles involved in the muscular rigidity and mechanical reflexes of a "decerebrate" animal, namely, that intensity of consciousness ("going to matter") and muscular differentiation and fluidity are closely related. Learning to visualize and move in patterns of unaccustomed complexity and sensitivity prepare the actor to present his new nature to the public.

Reich's emphasis on the complex interactions of muscles and awareness makes the same point. Our feeling at Blake College is that the human substance itself is involved in education, and that we work on ourselves as we work on our various projects.

"Culture" can be understood as the perceived limits of possibility. Class interests have been responsible for the "classical," static view in which man's capacities are limited in ways that justify exploitation. Other energy problems, e.g., diseases of age or poor nutrition, may harden the perceived limits of possibility. Just speaking the language of a sick culture is a threat to the naturally flexible perceptions, unless "innocence is organized" by a kind of paranoia that guards against limited desires and perceptions. Our work, of expanding our perceptions, and others',

requires a lot of different techniques, but the process can be described generally as the complexification of matter and consciousness through what Blake called "Mental War."

Education as Advertised in Napoleonic Times

The Suffolk Review, September, 1984

An etching by Gillray from a watercolour by an amateur, published 1st January 1809, undoubtedly gives an excellent clue as to the market at which many of the small educational advertisements in the *Ipswich Journal* were aimed.

These advertisements usually provide the following items of information: The name and address of the Principal(s), the Terms (financial and/or temporal), the Curriculum and Staff required. From this information, from cartoons and other sources an impression of education in the Napoleonic era can begin to be formed.

Many of the advertisements only run to two or three lines, but by superimposing information from a series inserted by the more regular customers we can sometimes get a glimpse of how these establishments thrived, what they taught and the fees they charged.

James Potter's school at Tuddenham, near Barton Mills had, in 1785, "27 Scholars and daily expected 2 Boarders." In 1792 James was advertising for an apprentice for three to five years and he expected a premium for providing this experience. Elsewhere in the same paper he announces the award of a silver pen to one of his pupils for writing. Both these practices are to be encountered in advertisements for several other schools.

Looking at James' letters we can see that his spelling did not match his penmanship—he "proberbaly" spelt as he spoke and that may have had its defects.[†] Dr. William King, son of one of Ipswich School's Masters, wrote about another man: "The name of our writing master was Harmer. He wrote a good hand himself and taught us to write in a steady firm hand. He took quantities of snuff. Young as we were we quizzed him for his 'h'; he always put it in and left it out in the wrong place, like Dr. Rose of Penang."[‡]

When James Potter died in 1806, Tuddenham School was advertised for sale by Auction by Robert Isaacson. Reading the list of Household Furniture is like a prospective parent being taken on a conducted tour

[†] James Potter's letter dated Feb. 1st, 1785 S.R.O.

[‡] MS Autobiography of William King M.A., M.D., F.R.C.S. (1786–1865) S.R.O. S/92/KIN/16284.

of the establishment and it is clear that the Potters lived in considerable comfort. The school must have been mainly self supporting in dairy and agricultural products—as indeed would have been generally expected in a country school:

TUDDENHAM SCHOOL

Near Barton Mills in the County of Suffolk

To be SOLD by AUCTION

By ROBERT ISAACSON

(Upon the premises)

On Thursday, July 24th and following days.

The valuable Household Furniture, Farming Implements, hay stover, growing crops of corn, and other effects, of the late Mr. JAMES POTTER, deceased. The Furniture comprises 19 sacken-bottom and bureau bedsteads, 16 well seasoned feather beds and bolsters, 38 blankets, 20 quilts and coverlets; pair of handsome mahogany dining tables, mahogany chairs with needlework seats and covers good Scotch carpet 4 yards square, wainscot dining and pillar tables, handsome Windsor, kitchen and chamber chairs, pier and dressing glasses, 7 desks and 11 forms; quantity of china, glass and earthenware, boilers, saucepans, kettles, &c; brewing and washing coppers, sound and sweet beer casks, mash and wort tubs, very excellent small barrel churn, and other dairy requisites, glass bottles, &c, &c.

The Farming Stock consists of 3 very excellent milch cows, weanel calf, 1 of the best and most useful mares in the neighbourhood, 7 years old, new tumbrel cart, and a half load ditto, nearly new, foot plough, stetch harrow, roll, excellent cart and plough, harness, sow in pig and three shoats; about 8 tons of rare stover, got up in the best condition, a quantity of manure, corn screen, bushel, chaff box, &c. 4 acres of oats, 1 1/2 acre of rye, half a load of rye straw, and a very neat taxed cart and harness, little worse for wear.

Catalogues to be had at the Hall, Barton Mills and Kentford; Bell, Mildenhall; Hope, Chippenham; Chequers, Worlington;

> *Griffin, Isleham; Green Dragon, Fordham; Red Lion, Newmarket; place of Sale; and of Mr R Isaacson, Auctioneer and Appraiser, Oak Farm, Cowlinge, near Newmarket. The sale to begin each day at 10 o'clock precisely.*

Some enterprising principals started an academy in one place and then, when it had established some reputation, opened another elsewhere, reaping the rewards from both. In 1800, Miss Beck and Miss Marsault announced their intention of opening an establishment for Young Ladies at Coddenham. They had both come from Mrs. Carter's seminary "at Lambeth near London." That this venture prospered can be seen from the announcement in 1806 that they were moving at Michaelmas to larger premises in Needham Market and we are left wondering whether their former assistants, Mrs. Howard and her daughter, continued to be as successful in running the Coddenham School. They were, for only a year later we find these good ladies advertising for an Assistant who "perfectly understands the English Language, Fancy Work, &c. None need apply who have not been in that capacity for some time." So it appears the school was thriving.

Cost of education in such seminaries varied considerably and depended on two main factors: age of pupils and type of tuition. In addition, "extras" could mount up rapidly—a financial trend not unknown in more modern times! As the war dragged on and the cost of living rose, so school fees increased. The Rev. T. Tennant, Curate of Claydon and Akenham, charged 12 to 18 guineas per annum in 1798[†] and 16 to 20 the following year.[‡] It is impossible to tell which increases were due to a school meeting with success and the proprietor feeling he could "get away" with an increase and which were genuinely due to the cost of living. Entrance fees were usually expected and varied from half a guinea to about five. At Mr. Tennant's school, the entrance fee was one guinea to the Master and five shillings for the Usher, one of the establishments for "Young Ladies" waived the entrance fee if one had already been paid to another school—this may well have proved an attraction when officers and their families for instance were moved from one garrison to another.

One advertisement for the Classical School at Beccles exemplifies the price of exclusiveness: "Where wine, tea and a single bed will be

[†] *Ipswich Journal*, January 1st, 1798.
[‡] *Ipswich Journal*, January 5th, 1799.

expected, an hundred guineas per annum."† More frequently, however, it is washing that is mentioned: "Washing not included," "Washing paid for separately," or even "Washing 12 shillings per annum." Since vacations were, on average, about a month at Christmas and a month at midsummer, this meant 12 shillings for 10 months washing.

Muriel Clegg writes that "the terms 'young ladies' and 'young gentlemen' conjure up notions of finishing schools, when in reality children of six to fourteen were being provided for."‡ The Preparatory School at Eye, run by Frances and Mary Reeve in 1801 proposed accepting "young Ladies and Gentlemen" aged three to five: Mrs. Cole of Ipswich took "12 Young Gentlemen" aged three to six to "prepare them for a gentleman's school," while Mrs. Batchelor at Wickham Market ran a preparatory school for "young Ladies under eight."

If we should feel this age range is exceptionally young, we should remember that the practice of parents separating from their offspring is different. In *A Portrait of Jane Austen* Lord David Cecil tells us that the Austen children "according to the custom of the time, were at first put out to nurse at neighbouring cottages,"[1, p. 29] though he makes it clear that in the Austen's case they were seen daily by their parents. Other families at that time may not have been so particular in this respect. Furthermore, "Young Gentlemen" frequently became Midshipmen in the Royal Navy at 12, as two of Jane Austen's brothers did, and so, indeed, did Horatio Nelson.

In any case these preparatory schools met with Dr. William King's approval. He was the son of the Rev John King, sometime Master of Ipswich School and had attended both Ipswich and Westminster in his own schooldays. Writing in the 1860's of his own early years, he comments, not without a justifiable degree of Victorian complacency, that:

> *One of the greatest improvements of the age is the preparatory classical schools, in which the young are separated from the old, so that they can neither be bullied, (nor) learn their vice in language or other things. The next great improvement is single beds for health, comfort and propriety. At Westminster I had*

† *Ipswich Journal*, January 8th, 1803.
‡ Muriel Clegg, *Suffolk Review*, Vol. 5 No. 2, p. 70.

> *to pay five guineas a year for a single bed. The Ipswich school had not arrived at that pitch of refinement. Most of the beds were double. With little boys this did not so much signify: but when a little boy of 8 or 9 was made to sleep with a big boy, he was liable to be bullied and dare not much complain. I believe my father afterwards thought this a great error in education. In those days I believe it (was usual) for grown up people to sleep two in a bed. Female servants often do it now: and I believe men servants often did it then. During the last 50 years we have improved in all kinds of comfort, health and propriety. Medical science has acted beneficially upon all departments of life, personal cleanliness, ventilation, fresh air, diet, sleeping apartments: to say nothing of water and sewage.*[†]

We cannot always tell from the advertisements whether the establishments were for boys or girls or whether day scholars were accepted as well as boarders, though the Rev. Tennant's entry for 1800 specifically states that "No day scholar permitted to associate" and the Rev. N. Redit of Grundisburgh advertised boarding accommodation for Young Gentlemen with "accommodation for Young Ladies in separate apartments."

It was on the point of boarding accommodation that Endowed or Charity Schools and Private Enterprise Establishments overlapped, for many of the charitable foundations allowed, not to say encouraged, the Master to augment his salary by accepting boarders, so that the word "Free" in a school's name frequently only applied to a minority of pupils. On the other hand, there were some foundations that stipulated that the Master should not be the holder of a benefice lest the duties should in any way conflict.

> *EDUCATION*
>
> *The FREE Grammar School at Botesdale, having lately been repaired and fitted up for the reception of boarders, will be opened the 23d inst., where young gentlemen are qualified for the University, the Professions, and Trade by the Rev. Wm. HEPWORTH. Terms twenty guineas per annum. Entrance One*

[†] MS Autobiography of William King M.A., M.D., F.R.C.S. (1786–1865) S.R.O. S/92/KIN/16284.

Guinea. N.B. French, Dancing and Drawing by proper Masters.[†]

Twenty guineas was a considerable amount of money in those days, but it appears to have been a fairly average charge. The basic fee for young ladies at this time was in many cases less, but whether when all the extras were added in, there was very much difference, is open to doubt.

The terms for the Dedham Grammar School at Christmas 1815 provide what is perhaps a representative example:

Dedham Grammar School

Xmas 1815

	£	s	d
Admission	0	0	0
Board & Tuition, Writing, Arithmetic, &c.	39	18	0
Washing	3	3	0
School Bill £	43	1	0
Books & Stationary	7	15	7
Allowances, &c. per Account			
Surgeon & Apocathary	2	13	0
Dancing Master	8	8	0
French Master			
Taylor	1	16	2
Shoemaker	1	13	2
Carpenter	0	12	2
Glazier	0	5	6
£	66	4	5

School will open on 27 Jan 1816

Letter this 18 Dec 1816

Her Richardson

As for the subjects taught, one or two points should be made. The Dancing Master (nicknamed the "Hop Merchant" or "Caper Merchant" by irreverent youngsters[2, p. 62]), not only taught the steps of the minuet,

[†] *Ipswich Journal*, July 31st, 1792.

but also gave instruction in "deportment," a "vital accomplishment" in a "genteel" education, and, particularly in the early years of the period, also taught fencing in many cases.

The Writing Master, besides the loops and pot-hooks one might expect, also taught his pupils how to sharpen quills and generally care for the pens. This is clearly shown in advertisement inserted by G. Harmer (son of the snuff-taking Harmer referred to earlier) in 1812, offering pens for sale at prices from 4 to 10 shillings per 100 and guaranteeing satisfaction and offering due after-care. This was doubtless a profitable side-line, for a schoolmaster's was not a very lucrative vocation. In many cases it was only by combining the office of schoolmaster with those of parish clerk and sexton that the poor fellow could make both ends meet. "Writing in all the usual hands" appears frequently. In commercial courses this sometimes included shorthand, but more usually meant such scripts as Italic (favoured by the ladies), Large Court and Running Court, (used by diplomatic and legal people) and Coursive or Running Hand, which was what most people favoured. Though copy-books sometimes included such exotic scripts, as Syriac, Armenian, Muscovian and so on, it is extremely unlikely that even Hebrew would be seen in writing schools outside London, though Latin and Greek alphabets would be taught in all Grammar Schools.

Surveying skills were in great demand in the age of enclosures, canals and turnpikes. Many schools advertised surveying and some, especially in ports, also taught navigation. Sometimes these subjects were regarded as branches of "the Mathematics."

Drawing was an important accomplishment. Naval officers were encouraged to keep a sketch book of coastlines and harbour entries and Army officers frequently needed to draw pictures of fortifications. Besides this, a talent for portraiture or cutting a neat silhouette was a real acquisition in pre-camera times and botanical drawings featured in many scientific and travel books.

"Use of the Globes" (elementary Astronomy) was seen as a subject suitable for both sexes for "Terrestrial and celestial globes have always been prestige items, and were the basic furniture of the gentleman's library irrespective of whether he knew one end of a telescope from the other or whether the tropics were fashionable diseases or not."[3]

Besides the "Use of the Globes," young ladies were also instructed in, Geography and Fancy Work or Needlework intended to demonstrate

the various sorts of stitches (hence the Sampler)[4] but courses in Natural Philosophy (Science) were almost exclusively the perquisite of male education.

Schoolmasters were supposed to be licensed to teach, though no such requirement was expected of the ladies. "Failure resulted in loss and forfeiture of office. Such an offender was to be 'utterly disabled, and (ipso facto) deprived and the place void' as if such person so failing were naturally dead. 'For the first offence the penalty was three months imprisonment without bail, for the second, three months and a fine of £5.'"[5]

It appears from the Diocesan Registrar's seal fee book 1751–1810 that for the whole of this period the fee was 7s. 6d., for schoolmasters' licences. It is possible that other fees were charged, recorded elsewhere, but this was probably the main expense. However, there is considerable discrepancy between the lists of people who advertised in the *Ipswich Journal* and the list of names appearing in the Subscription Books, but there do not seem to be any cases where a schoolmaster was prosecuted for failing to have a licence.

Most of the Masterships of the Grammar Schools and many of the Endowed schools went to graduates, in East Anglia this usually meant Cambridge graduates, and the licences accordingly read "Licences to the (Free) Grammar School at…" Sometimes such a Mastership disqualified the recipient from holding a benefice. In the 1770s and 1780s licences frequently read "to keep an English School to teach Reading, Writing & Arithmetick," a little later "to Teach English Grammatically." In 1785 there was a spate of licences "to Teach School," in 1791, some licences read "to teach Grammar & the Catechism of the Church of England," and there is one very unusual example in 1794 when James Pyman was licenced "to teach & instruct Grammar, the Catechism of the Church of England & Other lawful & honest Documents" in the parish of Earl Stonham.

In an age when flogging was rife in the Army and Navy, it is not surprising that many schoolmasters made extensive use of corporal punishment, thus earning the nickname "flaybbttomists,"[6] (the Bishop's Register of Licences included "Curates, Schoolmasters, Surgeons, Midwives and Phlebotomists"), but "standing in the corner" and "Dunce's caps" were also used, as several pictures of those times show. On the other side of the scale, Silver Pens were awarded in a considerable num-

ber of these establishments as we have seen at James Potter's school (a tradition still maintained at the Skinners' School at Tonbridge), which dates back to its foundation in the 1560s, where the original cost was "two shillings and sixpence, two shillings, and twenty pence" for 1st, 2nd, and 3rd prizes respectively and "nowadays is of the order of £300 inclusive of engraving and presentation cases."†

What of the schoolmasters themselves? From the newspapers we can gain some insights into the hazards of the occupation of schoolmasters and of the dangers facing some pupils, of which these examples are illustrative: Edward Ford and John Dunthorne may or may not be typical, however:

> *Mrs. Ford very respectfully informs the Inhabitants of Ipswich and its neighbourhood, that some particular circumstances having compelled her husband to quit his school, whereby she is left with her family unprovided for, she is determined to continue it under the care of an able Master, having been so advised by some of her most respectable friends, who have kindly promised her their support…*
>
> *Mrs. Ford begs Leave to acknowledge most gratefully, the encouragement and support she has experienced from her friends, and having now opened the School under the care of a master every way qualified, hopes for the continuance of their favours. Terms for Boarders as usual. Day Scholars, 10s. 6d. per quarter.*

In November 1799 "The Commissioners in a commission of Bankrupt awarded against EDWARD FORD …schoolmaster, stationer, dealer and chapman" were meeting at the Bear & Crown to take the last examination of the Bankrupt.‡ Bankruptcy was very common at that time in all walks of life and Ford was not the only schoolmaster to experience it.

Whether this influenced John Bransby to leave teaching or not we shall probably never know, but in September of the same year he purchased "the HOUSE and SHOP now in possession of Mr. Forster,

† Information supplied by J. Parsons, Schools Clerk to the Governors of Tonbridge School.

‡ *Ipswich Journal*, July 27th, August 10th, November 16th, 1799.

bookseller, stationer and dealer in medicines, whom he is to succeed on Monday next" and "Returns thanks to those Friends who have entrusted him with the Education of their Children, and takes the liberty of recommending Mr. B. Strutt, his successor in the school."†

Whereupon John Bransby continued to flourish, thriving, no doubt, on the proceeds of medicines sold to troops returning from Walcheren, various surveying jobs and a pamphlet of observations and calculation on Hailey's Comet some ten years later. Whether Mr. Strutt thrived also we do not know.

In 1810 we read in both the *Ipswich Journal* and the *Suffolk Chronicle* of John Dunthorne, the schoolmaster at Dennington, being tried at the Quarter Sessions for "gross and indecent assaults upon several of his female pupils" being sentenced to pay a fine of 40s. to the King, for each offence, to be imprisoned for two years in the County Gaol and to stand in the pillory, in the market place, in Ipswich on the last Saturday of December of each year. Dunthorne appeared to be in his fifties. That he survived his punishment we know from the following entry in the *Ipswich Journal* in February, 1812:

> *Yesterday John Dunthorne, the schoolmaster of Dennington, was discharged from the County Gaol in this town having received a free pardon.*

† *Ipswich Journal*, September 28th, 1799.

Emprise Should Evaluate Conventional and Alternative Treatments Comparatively

Townsend Letter for Doctors, May, 1990

I hope you will be able to engage the Emprise people in a dialogue on the various approaches to cancer therapy. I think some of the people who seem so rabidly opposed to any therapy that deviates from the "standard" therapy of the moment are just misled by the claims that seem to be accepted by "all the respected authorities."

Several years ago there was a lot of publicity about the great improvement in the rate of cancer cures in recent decades, but someone pointed out that the death rate from cancer hadn't improved at all. About 20 years ago, Harry Rubin (an honest researcher in cancer-related matters) pointed out that if you aggressively hunt for cancer in any symptom-free 50 year-old person, you are likely to find it, since autopsies show identifiable cancer cells in everyone of that age. If refined techniques of screening for cancer (such as whole-body MRI) are developed, we can theoretically get extremely high "cure" rates without lowering the death rate at all.

Until recently, the American Cancer Society continued to base its propaganda on a weird procedure called "age standardizing on 1940," but they have stopped that. The post-war baby boom made the average population younger for a few decades, but now the birth-control pill is making the average population older. In this situation, the trick of comparing the death rate for childhood cancer in, for example, 1950, to the rate in 1986, would make it appear that childhood cancer was being defeated, just as the 1940 reference made it seem that the rate for old people has been improving.

Even the A.C.S. admits that radiation causes leukemia and other cancers, but they are apparently not interested in the effects of fallout from nuclear bomb tests on the leukemia death rate. Anyone who is sure that childhood cancer is being conquered by chemotherapy should consider Ernest Sternglass's discussion of the effects of radiation exposure on the incidence of miscarriages, congenital hypothyroidism and other birth defects, leukemia, brain cancer, and brain development. Since the 1963 agreement to stop atmospheric testing radiation exposure has been decreasing, and so I would expect a real decrease in the childhood

leukemia incidence. If you added a real decrease in incidence to the decreased percentage of children in the population, you could get a nice fat decrease in the deaths-per-100,000-population.

I have read widely in the conventional cancer literature, and I think the research is generally crummy, with a shockingly high proportion of what looks like deliberate distortion. It takes a long time to form a picture of what is going on in a particular area of research, unless you have some clues to begin with. A group like Emprise could do exactly the same thing for conventional therapies that they are doing for alternative therapies. This would make their work more credible.

Many people who were about to submit to a "standard" treatment have asked me for my opinion, and when I tell them they ought to read the research that their doctor feels is decisively in favor of the treatment, many of them decide not to proceed with that treatment. A few times I have given people reference to publications in the hospital library, and their doctors have refused to give them permission to use the library. I'm sure that an extensive and coherent compilation and evaluation of the scientific basis of conventional medicine would wreak at least a little havoc.

Energy, Entropy and Estrogens in Aging

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In my study of aging-changes in oxidative metabolism, around 1970 I began to notice parallels between aging and the effects of estrogens. Investigating further, it appeared that an energy deficit was the common factor, and that many harmful factors, including radiation and hypoxia, caused a similar pattern of changes. (Reference 1.)

A variety of biophysical methods (NMR and ESR of living tissue, whole-cell electrophoresis, the influence of electromagnetic fields on nerve cell latent periods, etc.) led me to interpret the biochemical changes occurring in various tissues in aging, hypoxia, and estrogen dominance as a coherent response of the cells to disorder resulting from an excess expenditure of energy.[1–3]

In 1971 I suggested that progesterone and related steroids would have anti-aging properties deriving from their effects on the structure of cell water and the energy charge of cell.[3,4]

The same pattern of estrogen dominance is seen in both sexes with aging, and in all species studied. The anti-estrogens, especially progesterone and dehydroepiandrosterone (DHEA) decline similarly with age in both sexes.

Since 1971, I have worked out the physiological implications of this approach, as I will describe briefly below, and I have tested the ideas in a wide variety of age-retaled conditions in humans, including (1) Alzheimer's disease and Parkinson's disease and other "senile" changes in nerve function, (2) a variety of senile degenerative skin changes (3) changes in the circulatory system including arrhythmia, hypertension, gangrene of the feet and putative "stroke," (4) changes in bones including osteoporosis and arthritis, and (5) changes in respiratory function, including emphysema-like changes appearing in old age.

Progesterone and other "anti-estrogens" have caused rapid and thorough recovery from many of the diseases which are widely considered to be the unavoidable consequences of aging. "Auto-immune" diseases have also been treated successfully, regardless of age.[5,6]

Many of the metabolic consequences of stress tend to create vicious circles of self-stimulating processes of decline, on both the cellular and

the systemic levels. The work of F. Z. Meyerson, especially his concept of the "calcium triad," contributes powerful support to this view.

On the cellular level, in aging and estrogen-dominance, Magnesium-ATP tends to be lost as calcium is retained in excess. The sodium-potassium-ATPase activity declines. Proteolysis increasingly dominates relative to protein synthesis. Repolarization of nerve, muscle, and secretory cell tends to be retarded, causing such diverse events as "elevated hypothalamis thresholds," coronary vasospasm, insomnia, hallucinations, delayed T-wave in the electrocardiogram, and leg cramps. Ammonia tends to appear in tissues in these states, as protein catabolism dominates.

On the systemic level in aging, estrogenic effects are evident: a tendency toward prolactinoma, toxic effects of prolactin on kidneys and other organs affecting water balance, disturbance of thyroid function, adrenal compensation or exhaustion, atrophy of muscle, skin, and other tissues. Prostate hypertrophy now appears to involve estrogen dominance, and to be reversible with progesterone treatment. Reduced sensitivity to CO_2 in the blood, and diminished gas diffusion in the lung also occur very frequently. Bowel function is altered by prolactin toxicity, and by other degenerative changes.

Since certain environmental events relate clearly to the patterned metabolic changes mentioned above, those events must be considered.

Animals of very different types migrate to higher latitudes for reproduction. At high latitudes the effect of the vernal increase of photoperiod becomes intensified. The light-induced hormonal changes which increase fertility also increase general vitality and decrease the problems associated with aging. The hormonal changes occuring in winter and at night aggravate degenerative processes and increase mortality in all of the species that have been studied, including humans, in spite of the use of artificial lights. Certain age-related conditions, especially osteoporosis and depression, can be alleviated with artificial illumination. It has been established that darkness is associated with diminished anti-estrogens, and with elevation of prolactin and cortisone. The normal diurnal cycle appears to be a factor in aging.

Loss of muscular tone in the bowel is associated with aging, and increases the likelihood of exposure to bacterial endotoxin and to bacterial anti-thyroid substances, and increases the antigen burden. Permeability of the bowel wall is increased by stress, and forms part of another vicious circle, promoting degenerative changes. These degenerative changes can

be reversed partly by treatment with hormones, but the altered bowel flora is a problem which requires further research.

Treatment with progesterone and other anti-estrogens has reversed a variety of age-related changes in humans and in experimental animals, and has extended the life-span of experimental animals.

A useful theory of aging should include three levels: cellular chemistry, physiology, and the relation of the organism to its environments. All of these levels can be involved in self-stimulating processes, stabilizing the organism at different levels of energy and entropy in such a way as to make degenerative changes appear to be irreversible. Nevertheless, intervention at certain points to reverse disorder is possible.

Projected research: I am investigating the biochemistry, and potential therapeutic use, of substances which seem to directly or indirectly promote cellular order, repolarization, and sensitivity to biological signals. To further rationalize chemical therapy for aging and its complications, I will try to determine the mechanisms by which extended photoperiods promote the desirable hormones. This will involve (1) examination of the effects of light on DHEA levels (2), the effects of photoperiod on intestinal flora, and (3) investigation of physical-chemical changes in light sensitive tissues during stimulation.

Energy, Structure, and Carbon Dioxide

A Realistic View of the Organism

Ray Peat's Newsletter, 2013

WHAT could be more important to understand than biological energy? Thought, growth, movement, every philosophical and practical issue involves the nature of biological energy. The question of biological energy is usually handled in the manner of the cosmologist who explained that the earth rests on the back of an elephant; when asked what the elephant stood on, the cosmologist replied that "it's elephants all the way down." Several decades ago, it was discovered that ATP mediates many processes in the energized cell, but there is still fundamental disagreement on the question of how ATP is synthesized, and how its energy is used to produce movement, to control the movement of water in cells and organs and to regulate the ionic balance of cells and fluids, and even why its absence produces rigor mortis.

When people actually try to examine the question of how the "high energy bond" of ATP can be transformed into usable energy, they sometimes find that it is easier to propose fundamental changes in the laws of physics than to find an explanation within ordinary physics and chemistry.[1] More often, biologists simply prefer not to go beyond the first or second elephant.

However, there is a way of looking at the nature of life that doesn't involve mythical beings. The writing of history, in science as in politics, is often an ad hoc convenience, usually done to achieve maximum self-justification. When Harry Truman announced that he had dropped an atomic bomb on "Hiroshima, a military base," he was revising, for a moment, the history and geography of Japan. Usually, fictional histories created by powerful institutions become part of a general culture, and are relatively permanent. "Scientific revolutions" and "paradigm shifts" are just tardy acknowledgments of the silliness of the ruling fiction. In the process of accepting a slightly more rational way of doing things, those who have reluctantly given up the old doctrine will look for ways to show that they were on the right track all the time, that all of the nonsense was necessary. They want to maintain the illusion that scientists are intelligent and rational, for the same reason politicians want to create the

illusion that they are just and wise. Television networks and newspapers agree that genocide is exactly where the president says it is, because they and the president have common interests; likewise, science journals and textbooks are there to protect the orthodox beliefs of institutionalized science, much more than to search for truth. For historical doctrinaire reasons, Aristotle's ideas and the culture that had been built up around them were practically eliminated from Anglo-American culture a few hundred years ago. In Aristotle's "formative principle," nature itself was creative and purposive, "teleological." His ideas, and the people who held similar ideas, were suppressed because of the dangerously democratic implications seen in them by the ruling classes. Since Ilya Prigogine's Nobel Prize, a false cultural history of "emergence" has been formulated, to derive the idea of the sudden appearance of order out of disorder, from the official anti-teleological (platonistic) rationalism that had seen change as a matter of random fluctuations in a time-reversible system, in which numbers are real and substance is unreal. In this new version of history, cybernetics is blended with neodarwinism, to explain order as something external to matter, and dependent on chance rather than purpose.

Since I was following N. A. Kozyrev's work (on stellar and planetary energy) from the late fifties through the sixties, I thought of volcanism as a process essentially equivalent to solar energy. Then, in 1968, I read Sidney Fox's experiments with heated amino acids, and saw that volcanism was a more appropriate energy than sunlight for driving the origin of life. In some of his experiments, Fox put nearly dry amino acids onto hot volcanic rocks, and when he added a little water, the amino acids polymerized spontaneously, and nonrandomly, into peptide chains; when these were put into water, they spontaneously formed microspheres, that looked like, and behaved very much like, bacteria. Fox saw his work as a validation of the principle that nature itself created higher order spontaneously.

Deep in the volcanic earth, or deep in the ocean, life would be protected from destructive ultraviolet radiation, whether or not the atmosphere contained enough oxygen/ozone to screen out that radiation. And thinking about volcanoes, I questioned the idea that life had to originate in the "reducing atmosphere" that was dogmatically required by the conventional protobiologists. Volcanoes emit water, carbon dioxide, and

a variety of strong oxidants. I think it is possible that atmospheric oxygen preceded green plants.

If Sidney Fox's spontaneously formed proteins and microspheres are similar to the original living cells, these forms of life appearing in volcanic seeps would have originated in an environment rich in carbon dioxide, and I have gradually come to imagine that the present ordinary respiration based on oxygen might have originated as an adaptation to an environment deficient in carbon dioxide, as life spread out from its volcanic origins.

The history linking volcanic life to contemporary sun-based life is still in doubt, but in outline we can think of the sun as a present energy source, and the chemistry of the earth as, relatively, an energy sink. Electrons activated by light energy from the sun give up that energy, as they move through various steps until they combine with oxygen. Energy flow, in this sense, is somewhat like the energy flow between the negative and the positive poles of a battery; ultimately, it produces heat, but in the process, it can produce work.

Life interposes itself between the "poles" of energy flow, and the flowing energy creates organization and structure, as it is dissipated into heat. Structures store some of the energy, and tend to increase in complexity, taking advantage of the flow of energy to create phase differences with expanded internal surfaces, like a finely mixed emulsion. Like a finely divided emulsion, the more highly energized the organism is, the stabler it is. It adapts to the available energy; energy is used in adaptation; the structures built with the energy are adaptive structures.

This idea of the development of organismic complexity as a response to conditions that are "far from equilibrium" was first clearly stated by V. I. Vernadsky, about 80 years ago, but now the idea is associated with Ilya Prigogine. The only difference is that Prigogine has inserted an element of indeterminacy, which seems to have ideological appeal for much of the academic world.

In Fox's production of the proteinoid microspheres, the ordered growth is a consequence of the properties of the substance in a permissive environment. The order is not imposed from the outside onto passive matter. When Darwin was a university student, he accepted Paley's doctrine of "Natural Theology," in which a watchmaker god inserted design into the material world. As he matured, he allowed for a certain Lamarckian intrinsic process of ordering, but he emphasized the role of

natural selection, in which the design was imposed by the environment, in the same way that animal or plant breeders use artificial selection to impose the traits they want. The neodarwinist movement "corrected" Darwin, putting all of the responsibility for the "design" of organisms onto the natural selection of strictly random variations. The cybernetic culture is having a strong influence on neodarwinism, and some of the new histories of science that are being written are trying to place the design process on the abstract mathematical level, rather than looking for it in the nature of substances. Devotees of "chaos theory" would entirely displace the designing principle from the material world. The meaning, and the effects, of this process of mathematizing neodarwinism are antagonistic to the facts demonstrated by Sidney Fox's experiments, and are tending to move research farther away from the creative nature of life.

Despite the present emphasis in "nonlinear dynamics" on random fluctuations and instabilities, the fact is that complex organisms, and finely mixed emulsions, are very stable, and the direction of their development is essentially determinate. Vernadsky described this fact as a law of evolution, that organisms and systems would tend toward the production of a high metabolic rate and large size. This means that evolution tends toward a maximum of energy use, a maximum of adaptive structures. The brain is the dominant organ of adaptation, and the evolutionary tendency toward "cephalization" is an illustration of Vernadsky's law.

The stability of the fine emulsion, or of the evolved organism (a person has greater homeostatic powers than a rat), involves the fact that, within a given range of available energy, the very complex structure has dissipated the energy within itself to a high degree. Every point of the system has come very close to being in equilibrium. It's a situation analogous to that of a road that climbs a mountain with a nearly infinite number of switchbacks—as the number of switchbacks tends toward a maximum, the slope of the road at any point tends toward a minimum.

Mammalian cells are smaller than frog cells; we are like a well homogenized emulsion, compared to animals with lower rates of metabolism. An unstimulated cell is practically in equilibrium with its environment. This is the "high energy resting state." Activity generates structure, but when a cell is inactive, it is stable and doesn't have to expend energy. This is exactly contrary to the doctrine in which a "cell membrane" maintains

the cell's organization by a constant expenditure of energy, running "pumps" to maintain differences in the ions and dissolved substances on the opposite sides of the membrane. In that doctrine, each cell, even at rest, is far from equilibrium; life is a struggle, and the cell must spend energy even to stay as it is. Gilbert Ling showed that the concept of membrane pumps to preserve the cell's order is both unnecessary and impossible. In the real organism, energy is spent to grow, to adapt, and to evolve, but not to merely persist.

If we understand Sidney Fox's spontaneously formed microspheres, I think we will get some insights into our own cells. For example, the microspheres have a remarkable uniformity of size, which they preserve even during growth, by dividing instead of simply enlarging. They tend to assemble into orderly chains, without coalescing with each other. They are stable in warm water, but dissolve in cold water. This indicates that the hydrophobic, "fatty" quality of the proteins, causes them to be expelled from the bulk water, forcing them into association with each other. Cold water has greater tolerance for fatty substances. The proteins, however, also contain regions that are water soluble, and when the proteins assemble into droplets, they continue to associate with a certain amount of water. This water is now "dissolved in the protein," in the sense that the properties of the protein are relatively dominant. (Bungenberg de Jong's studies of "complex coacervates" are still the best introduction to this subject.)

The modern practice of biochemists has been to extract soluble substances from cells, and to study them in dilute watery solutions, and then to believe that the things they observe in the test tube are the real properties of cells, of the "dilute solutions enclosed in a lipid membrane." If I hadn't had the experience of talking to dozens of biochemists who believed that no other kind of biochemistry was conceivable, I would find it hard to imagine that something like this could exist in a culture that defines itself as "scientific." Small particles have a large surface area in proportion to their mass. The balance, within the proteins, between hydrophilic and hydrophobic groups, will determine the proportion of surface area in contact with the bulk solvent water, relative to the mass of the microsphere droplet. More hydrophilic proteins will form smaller droplets, and at a certain point of hydrophilicity, will no longer form droplets. The temperature, by altering the structure of the water, inter-

acts with the hydrophilicity/hydrophobicity of the protein. Structures are generated as complex physical equilibria are achieved.

In our own cells, the microtubules, which are a part of the cell framework involved in cell division and movement, are dissolved at low temperatures, and are reformed when the temperature is raised. Some enzymes have this same temperature sensitivity. Since the water which is "dissolved in the proteins" of the cell is largely dominated by the proteins, its actions on microtubules and enzymes and other proteins will reflect both temperature and the influences of proteins and a variety of dissolved substances. Estrogen, for example, promotes the formation of microtubules, at a given temperature, as if it had made the water "wetter," or warmer.

When cells are stimulated, they adapt, with substance flowing into complexification until an approximate, appropriate equilibrium is reached. Stimulation is a need, and an opportunity, for adaptation and differentiation. If there is a need for adaptation, without the necessary substance and energy, the cell or organism will either deteriorate or withdraw. Polyunsaturated fats with inappropriate structure interfere with these adaptive flows of energy and substance in all of the known systems of cellular response. These exogenous substances suppress the respiratory energy system, the intercellular communication systems, and the intracellular response systems. Immunodeficiency, autoimmunity, inflammatory diseases, aging, cancer, heart disease, nervous diseases, and hormonal imbalances are produced when these fats interfere with the spontaneous self-regulatory processes of the organism.

When respiration is suppressed, the cell's production of carbon dioxide is suppressed. If we start with the best known example of carbon dioxide's effect on a protein, the Haldane-Bohr effect on hemoglobin, we will have a model for visualizing what happens to organisms in an environment that is poor in carbon dioxide, but rich in vegetable-derived unsaturated fats.

Carbon dioxide associates with protein in a variety of ways, but the best understood association is its reaction with an amino group, to form a carbamino group. In the presence of a large amount of carbon dioxide, the hemoglobin molecule changes its shape slightly, along with its electronic balance, in a way that favors the release of oxygen. The opposite happens in the presence of a high concentration of oxygen and a lower concentration of carbon dioxide. Other factors can modify the

effects of these gases on hemoglobin's shape, electronic properties, and its binding affinities. Wherever there is lysine or other free amino group (practically every protein and peptide), carbon dioxide can be expected to react with it to some degree, which will depend on other things in the environment. Lysine also reacts with sugars, so there is a competition between CO2 and glucose. In aging and diabetes, many proteins are altered by the inappropriate binding to sugars. There are enzymes which can remove sugars that have altered proteins, but these enzymes are inhibited by the presence of small fragments of starch molecules.

The absence of carbon dioxide bound to a protein is likely to have an effect on the protein's structure and function, but the presence of a relatively large sugar molecule, in a site normally occupied by carbon dioxide, will have drastic effects on the protein, including tending to solublize it, and to cause it to associate with its environment in other abnormal ways. In general, the presence or absence of carbon dioxide involves relatively quick and subtle changes in structure and function, analogous to the phosphorylation of proteins, but possibly competitive with it, while the presence and absence of sugars, as glycated or glycosylated proteins, tends to be relatively permanent, and to require enzymes to restore the original state. Carbon dioxide's regulatory effects have been studied in only a few enzymes and hormones, but there is enough evidence to show that its reactions with proteins and peptides constitute a major regulatory system.

The formation of carbon dioxide itself, from organic materials, has recently been demonstrated to provide the energy for synthesizing ATP.[2]

Around 1970, someone used a new technique that etched away the surface of a red blood cell, revealing an interior that was obviously highly structured, partitioned into orderly segments, but when I talked to biology professors, they still believed that a red blood cell was "just a bag of hemoglobin, enclosed in a lipid membrane." One of my biochemistry professors, who was smart enough to have opinions of his own, in private sarcastically referred to the "lipid bilayer membrane" as "the fat sandwich theory." But it would be several years before it became socially acceptable to talk about the cell's internal framework. Early in the century, before electron microscopes existed, a biologist had inserted tiny particles of carbon into cells under the microscope, and described their movement as they fell through the cytoplasm as resembling the movement of a pebble falling through a brush pile; it was obvious that

the clear cytoplasm was highly structured. The same biologist also rearranged the organelles within the cell, and demonstrated that they spontaneously returned to their normal positions. The cytoplasm can flow like a liquid, but it has some of the properties of a highly organized solid.

When I moved a microelectrode through a cell, using an apparatus that could move it forward or backward in very small increments, I found that the voltage fluctuated with the location in the cell, and that withdrawing or advancing the electrode, each location would show the same voltage as before, when the electrode returned. This meant that, even electrically, the cytoplasm was behaving as a solid, not as a liquid. According to the "membrane theory" of the cell, the liquid part of the cytoplasm has to have the same voltage in all of its parts. In that doctrine of a cell as "a drop of water containing dissolved molecules enclosed by a membrane," biochemists were required to think that enzyme-catalyzed reactions are governed by random collisions of the substances reacting with the enzymes, and that only a few properties of the solution, such as temperature, pH, and ionic strength, would have any influence on the behavior of the enzyme. Their doctrine seemed tenable to them, at the beginning of the 1970s, only because they had an essentially unscientific attitude that refused to consider the evidence, on the basis that valid evidence couldn't disagree with their position. In the case of hemoglobin, the idea that substances bound to the protein molecule could change its chemical and physical properties was accepted, and by analogy with that, additional "allosteric" (shape-changing) enzymes were beiing studied.

But, because of the commitments made to the "membrane enclosed cytoplasm" theory, the structural proteins were for a long time treated according to the rules established for enzyme chemistry—only local, random interactions were considered to govern their behavior.

In the 1950s, Gilbert Ling introduced a model of the cytoplasm that took account of its observable features. He called it the "Association-Induction" hypothesis. He proposed that substances such as ATP, hormones, and ions participated in cell physiology according to the ways that they associated with proteins and water, and that a powerfully adsorbed molecule, such as ATP, would influence the structural proteins in the cytoplasm as "cardinal adsorbants," altering the proteins' affinity for other adsorbed substances, such as potassium and sodium. The behavior of hemoglobin was a model for the behavior of the cytoplasm and its

components. Unfortunately, most biologists didn't even understand the role of adsorbants in hemoglobin's function, so practically no one bothered reading his work. The well-accepted fact of "backbone chemical shift" that results from something as simple as calcium binding to a protein is just another way of talking about the principle of association-induction. The actual chemical structure of the cytoplasmic framework in most types of cell had hardly been studied, and Ling concentrated on studies of the physiology of cells, treating the cytoplasm as an ensemble. Now that many cytoplasmic proteins are being studied in detail, the significance of his cell physiology can be seen more easily.

The "membrane" people like to talk about "ion channels" and "channel proteins," but they are simply describing fragmentary examples of the adsorption-induction process, in which strongly bound substances change the affinity of a protein for small ions and other associated substances. One of the effects of the membrane theory, and of studying enzymes dissolved in water, is that many biochemists got into the habit of thinking of proteins as water-loving materials; otherwise, why would they have to be enclosed by an oily membrane? But, in fact, proteins have a great affinity for fats. Fats are powerful regulatory substances. In excess, the wrong kind of fat associates with the cell framework, and alters that regulatory system, at the same time that it poisons enzymes and other functions.

Insoluble proteins tended to be discarded; sometimes they were called "membrane proteins"; when it turned out that the insoluble structural proteins often had "ATPase" functions, this enzyme came to be thought of as the "membrane pump." Even under ordinary assumptions about the way cells use ATP in their energy economy, Gilbert Ling showed that cells don't have the energetic capability of maintaining all of their gradients by "pumping" ions and other dissolved substances. But, the common idea that the phosphate bond in ATP is a very "high energy bond," with 14 kcal of energy, is an unfounded belief; in 1959, for example, Sidney Bernhard showed that a more realistic figure was around 4 kcal. But under relatively water free conditions, the bond forms spontaneously. One of the implications of this fact is that the control of water, the presence or absence of water, and the state of the water, is itself a matter of high-energy interactions. ATP does have a remarkably high energy of adsorption or binding to proteins, and this binding energy allows it to influence the protein's interactions with water. A very thin

layer of water between two objects can bind them together very tightly. The structures and movements in cells exist because of very specific interactions between large molecules, especially proteins, and the water which binds them and separates them. Both the water and the proteins are modified by the presence of carbon dioxide.

Two kinds of experiment show that the standard ideas about ATP and pumps have to be reconsidered. When muscles are stretched, they synthesize ATP;[3] this strongly suggests that its synthesis is a physica process, occurring in an environment in which water is inactive, allowing the reaction to be close to equilibrium. (In the heart, stretching has an anabolic effect.) In another experimental setup, the temperature is measured near the surface of a nerve; when the nerve is stimulated, the temperature rises momentarily above the starting temperature, but as the nerve recovers and repolarizes, the temperature falls below the ambient temperature. This "refrigeration," or heat absorption, isn't compatible with the activation of chemically powered "pumps" to restore the initial arrangement of ions, and it suggests something physically closer to the way that heat is emitted and absorbed by a rubber band when it is stretched and then relaxed. When heat production in a myelinated nerve is measured, the membrane theory would require that the heat production, like the electrical potential, should progress in a saltatory manner, jumping from one node to another, but the measurements showed that the heat production moves continuously along the nerve. This supports the idea that the bulk of the cytoplasm is undergoing a progressive phase transition.

Physically, all of these observations (which make no sense in the membrane theory) are compatible with a view of the cytoplasm as a cooperative molecular ensemble that is poised so that its alternative states are close to equilibrium, allowing it to spontaneously revert to its original state following a stimulus that changes its state slightly, or to cause systematic changes in chemical cycles which produce the substances, such as carbon dioxide and ATP, which tend to restore the original state. Nerve conduction, muscle contraction, and secretion are now recognized to involve the factors that cause "allosteric" shifts in molecular structure, association, and affinities. It is the myth of the cell as a "dilute solution organized by a membrane" that prevents the recognition that cell physiology consists primarily of such processes, coordinated into cooperative phase transitions. The recent discovery

that cell filaments form responsive systems extending from the cell's surface to the chromosomes makes it possible to see the process of genetic expression as an extension of this organized and unified system.

The standard doctrine about the structure of the membrane is that it is a lipid bilayer, meaning that an outer layer of fat (phospholipid) is arranged with its acidic water-soluble end turned outward toward the watery environment, and its fatty water-repellent tail turned inward, against the fatty tail of another layer of molecules, which has its acidic end turned inward, toward the supposedly watery cytoplasm. In support of this arrangement, an "oil loving" stain is applied to hardened cells (otherwise no membrane can be seen under the electron microscope), and a double line appears near the cell's surface. This is called the "lipid bilayer." However, since the theory says that the fatty parts of the two layers are pressed against each other, there is in the theory a continuous band of fat, separating two layers made up of the acidic heads of the molecules, and the theoretical structure of the "lipid bilayer" has no resemblance to the double line that is created by the stain. The material generally used to produce the image of a bilayer membrane is osmic acid, an oxidant; it wouldn't be expected to stain the layers of acidic heads of fat molecules. This might seem to be an embarrassing inconsistency, but apparently not to most scientists. After the electron microscope began making pictures of cells, it took some time to find the stain that would produce any membrane at all, and then it took about thirty years to learn to produce a "membrane" image that had a thickness that seemed appropriate for the theory. Considering the great effort required to produce a "membrane" image of the right size in the right location, they are willing to overlook the fact that the fat-loving stain hasn't quite found its way to the single band of fat between the acidic layers which their theory describes. Gilbert Ling described the boundary at the cell surface as a phase bouundary, of the sort that exists where two different materials meet, for example at an oil-water interface. When the two substances have different electrical-chemical properties, the forces between the phases move electrons and/or molecules near the surface into what is called an electric double- layer. Since stains have their own electrical and chemical properties, the stain molecules would be affected by the fields that produce an electric double-layer. Osmic acid would be expected to stain certain protein groups, including sulfhydryls and amines, which could be exposed in such an area of

strong fields. (Brain tissue that is deprived of oxygen stains diffusely with these "membrane" stains, suggesting that proteins are changing shape sufficiently to expose groups of this sort.) The forces between fat molecules, that allow them to form "hydrophobic bonds," are actually so weak that they should hardly be called "bonds," at least at normal temperatures. Fatty surfaces seem to seek each other out in a watery environment because water molecules bind so powerfully to each other that they tend to force out anything that doesn't bind to them. So, if we even consider the association between fat molecules as a "bond," it is the weakest bond that exists between any biological molecules. When a cell is attached to a surface, it can be torn to bits in trying to move it, without breaking its attachment to the surface. Obviously, it isn't attached to the surface by its "lipid bilayer membrane." The strength of a lipid bilayer would be limited by the extremely weak affinity of fat for fat; if you step on a sticky floor wearing tissue-paper slippers, your foot won't be ripped from your leg. A lipid bilayer has no more strength than the rainbow that forms on a puddle of water when a microscopic film of oil spreads over its surface. And the rainbow on the puddle is something that really exists.

Even though a cell's substance can flow, it has a cohesiveness that can greatly exceed that of ordinary watery solutions. The toughness of a steak isn't affected just by the extracellular connective tissue, as was once believed; the intracellular filamentous materials contribute greatly to its resistance.

Protein filaments can bind cells firmly to the materials that surround them, including other cells. Red blood cells normally float freely in a watery environment, but under some conditions they stack up into a rouleau, roll of coins, formation. The membrane theorists like to explain this pathological association in terms of ionic surface bonds, but experimentalists have pried the cells apart under the microscope, and photographed long extensible, apparently elastic, strands binding them together. The condition appears when the cells' energy is depleted, suggesting that the strands result from an alteration in the cells' internal framework. This kind of process would have practical application in the formation of a clot, producing strength and continuity that would be inconceivable if the red cell were "bags of hemoglobin enclosed in a lipid membrane."

If the cell's cytoplasm can be mechanically continuous with its environment, then the principle of allosterism, the conditionally responsive change of shape and affinities that is recognized in hemoglobin and some enzymes, has the potential for explaining the cell's ability to respond to its environment, and to alter that environment in a controlled way.

Filamentous, or other space-encompassing structures in effect are carriers and transmitters of fields of various kinds. A cooperative phase change (cooperativity means that a change which is slow to start will proceed quickly to completion once it gets started, because of interactions of its parts) can occur in a structure which has fluidity, so the signal transmitting function needn't be tied to mechanically fixed filaments. An ensemble of molecules can behave in a coherent manner resembling the behavior of hemoglobin. In fact, hemoglobin is a molecular ensemble which behaves cooperatively, as a functional unit, so there is nothing essentially novel in thinking about larger molecular ensembles making up the cytoplasm. Ions such as calcium are bound to oppositely charged ions, counter-ions, which are abundant on proteins. As the cell's state changes, calcium (and other) ions can be liberated from the binding proteins, and the momentarily high concentration of ions can serve to transmit an excited and activated state to other molecules, promoting enzyme activity, muscle contraction, nervous transmission, or other cell function. Not long ago, these movements of ions within the cell were explained in terms of membrane pumps and organelle membranes. Now, calcium-binding proteins and "channel proteins" have been dentified; the term "channel" derives from the idea that the impermeable membrane had to have pores for the entry and exit of ions and other substances. Supposedly "leakage" through those pores required pumps to compensate by moving substances in the opposite direction. At present, publications on ion channels are more than ten times as frequent as publications on their associated "membrane pumps." Many years ago, it was discovered that large numbers of sulfhydryl groups (a hydrogen bonded to a sulfur atom, which is often in the cysteine group of a protein) appeared during cell division. This represents a rapid and massive change in cell chemistry. The sulfhydryl group is ionizable, but in the late sixties and early seventies when the sulfhydryl shift still seemed important to biologists, there was no support for the idea that these groups could be involved in ion regulation, as part of Gilbert Ling's association-induction model of the cell. However, recently it has been

found that a "calcium channel protein" contains a cysteine group that ionizes during the molecule's change of state.[4]

Gradually, the idea of allosteric regulatory molecules that are altered by the reversible binding of regulatory substances has gained common acceptance, but the tendency is still to look for these signal receptors at the cell membrane and in association with the control of gene expression. But the cell filaments that make up the cytoskeleton are now known to form continuous systems from the cell surface, through the nuclear membrane, and into the vicinity of the chromosomes. These various filaments have "membrane-like" properties, allowing them to act at, and across, phase boundaries, but also making them sensitive to subtle changes in their environment, such as temperature, ionic balance, and the presence of fatty materials and materials combining various degrees of polarity in their structure; for example, the extremely toxic bacterial endotoxins are lipopolysaccharides, that derive their unique toxicity from the combination of fat and sugar in the same molecule.

For many years, the enzymes of glycolysis were the paradigm for the idea of random interactions between enzymes and their substrates, the materials they catalyze. They were thought to be the most random elements in a randomly organized system. Although it has been over ten years since Sidney Bernhard showed that these enzymes don't wait for their substrates to randomly diffuse into their active sites, this important fact is still generally ignored. (Others, from 1940 to 1998, have reported evidence that the enzymes of glycolysis are "bound to the cell framework.") The ordered behavior Bernhard demonstrated for these "most random" enzymes should be taken as a clue to the nature of other components of the cell.

Rather than having to transmit randomly received signals through random movements into the nucleus, the model of the cell that is implied by the work of Sidney Fox and Gilbert Ling is one in which "receptors" and "effectors" are distibuted throughout the cell substance. Rather than "feedback" of signals along channels of communication to processing centers, the processes of perception and response are distributed throughout a cooperative system, with the possiblity of response governing the process of judgment. There is intelligence in the system at every level, there is no coercion of stupid slave molecules. Fields, forms, associations, and movements all interact in a sensitive and responsive unity. At least they do in health.

In the process of an organism's development, the cell's form precedes its mature chemical functioning. The form depends on the internal framework, and that depends on the cell's contact with a specific kind of extracellular material. The matrix governs the basic pattern of gene expression, acting through the structural elements. In aging and stress, the matrix tends to deteriorate progressively. The matrix, being outside the cell, isn't constantly being renewed as the cell itself is, but it can be enzymically repaired, if the enzymes are not inhibited. Being located between the bloodstream and the metabolizing cells, it is necessarily exposed to all circulating environmental toxins.

There is a functional continuity between the extracellular matrix and the expression of genes.[5,6] This has been recognized for several decades by many researchers, but the doctrine of the cell membrane enclosing a watery solution has obstructed progress in this direction.

Some Implications

There is a chemical continuum from volcanic conditions to nerve cell structures and functions. The chemical precursors of life, ammonia, acetic acid, pyruvic acid, and amino acids are formed under volcanic conditions of high temperature and pressure. (Gunter Waächtershäuser, H. J. Morowitz, R. M. Hazen, and J. A. Brandes.) Under slightly milder conditions, amino acids spontaneously form proteins and self-replicating bacteria-like structures. (Sidney Fox, in the 1960s; Waächtershäuser[7] reported the synthesis of peptides, in a weirdly feeble parody of the work Fox did more than 30 years earlier.) Fox's spontaneously formed proteins improve nerve cell function—memory (in mice), and *in vitro* growth, survival (increased 250 %) and function, suggesting their functional similarity to ancient natural cellular proteins. Natural proteins become modified during development and stress, and these new primitive proteins might be interpreted by the cell as embryonic proteins, temporarily refreshing some cellular processes. The spontaneously formed protein structures are stable in warm water, and dissolve in cold water; microtubules and other fundamental cell components also "dissolve" when cooled. Formed in a hot environment, the synthetic proteins are biologically very compatible materials.

In this perspective, there is no point in which one has to insert an "assumption of randomness" into the process of cell formation or

functioning. The old idea of randomly arranged material, being ordered by the accumulation of random changes, was an idea that derived from the old concept of a watchmaker god inserting order into formless matter. In this more realistic perspective, the significant issue is what happens when disorder is introduced into the ordered cellular system. The introduction of disorder is a stimulus, a challenge to respond and to adapt. Excitation and assimilation, or excitotoxicity and degeneration, are two kinds of response to the introduction of disorder. Although the creation of order is a spontaneous tendency of the molecules, the introduction of disorder causes energetic changes that lead to the creation of a new order. The achievement of a new order builds on the old, emerges from the old, but contains the old order implicitly. The implicit presence of old structures accounts for the phenomena of memory, imprinting, transgenerational influences, and the recapitulation of phylogeny in development.

In the Randle effect (it's called the "Randle cycle," but there is no cycle), increasing the amount of fat in the bloodstream decreases the ability of cells to metabolize glucose; glucose tolerance decreases, as in diabetes, except that the response to fat is instantaneous.

Respiration decreases, mitochondria retain calcium, which tends to accumulate until it destroys the mitochondria. The calcium, when it is released from the mitochondria, causes excitation to increase. Stimulation without efficient energy production leads to proteolysis and apoptosis or other forms of cell death. Sugars replace carbon dioxide and acetate on lysines.

This process is involved in diabetes, Alzheimer's disease, arthritis, and other degenerative diseases, probably including osteoporosis. Mitochondrial damage tends to increase the production of lactic acid instead of carbon dioxide, and lactic acid can stimulate the inappropriate overgrowth of blood vessels, as occurs in the eyes in diabetes. During stress and aging, free fatty acids appear in the bloodstream in large quantities.

Besides their chemical effects, which lead indirectly to chronic disruption of signalling systems, the unsaturated fats have direct and immediate effects on regulatory processes, water uptake, intercellular communication, and excitation. Cell proteins have an affinity for fats, and their hydrophobic surfaces tend to adsorb them. Unsaturated fats have a greater affinity for water than saturated fats do, and the location

of the unsaturated bonds along the fat's carbon chain will affect the ways proteins interact with water. The fact that animal cells synthesize only fatty acids with a chain of eight fully saturated carbon atoms in their tails undoubtedly has something to do with the toxic effects of other unsaturated fats on the respiratory apparatus.

The unsaturated fats that are so systematically disruptive to warm-blooded animals are characteristically produced in plants at relatively low temperatures. In organisms that live at low temperatures, they probably serve a function (among others) that is analogous to the function of estrogen in warm animals, namely, raising the "structural temperature" of water, modifying chemical activity by liberating water to some extent from the domination of the cellular proteins.

One of the old theories of aging was that something (they called it metaplasm) accumulated in cells as a result of metabolism, the way ashes accumulate in a stove. Lipofuscin, or age- pigment, is related to the oxidation of unsaturated fats, and has been proposed to be such a material, that progressively limits a cell's adaptive capacity because of its physical and chemical properties. Amyloid, a clear mass of protein deposited in and around cells, is another such age or stress-related material, that is currently being studied in Alzheimer's disease and other degenerative diseases. Glycation, the attachment of sugars to groups that otherwise could be occupied by carbon dioxide, seems to be a crucial factor in the formation of amyloid. (The term "amyloid," in fact means "starch-like.") Changes in the extracellular matrix, for example the cross-linking of collagen molecules, have been thought to cause some of the characteristic changes of aging, and again, glycation is the major mechanism in the formation of cross-links.

In Alzheimer's disease, the commonly recognized features are tangles, amyloid deposits, hypometabolism, and evidence of inflammatory processes. Cells related to inflammation can produce amyloid, as well as remove it. Glycation, the attachment of sugar molecules to proteins, can happen quickly, and can occur either with or without enzyme catalysis. The failure of glucose consumption and of carbon dioxide production in Alzheimer's disease predisposes to glycation.

Glycation imitates mutated forms of proteins, for example normal transthyretin behaves like the prion protein, forming amyloid. Transthyretin, the protein that carries thyroid hormone and vitamin A, is normally taken up along with cholesterol under the influence of

thyroid hormone. Abnormal cholesterol metabolism is one of the traits associated with Alzheimer's disease. In the absence of thyroid-supported respiration, carbon dioxide and other respiration-associated molecules (e.g., acetate) are replaced by lactate and unused sugar, causing abnormal modifications of proteins such as tau, which regulates microtubule assembly. Glycation of collagen in the extracellular matrix alters the properties of the matrix. The glycated matrix would become a preferred site for glycated prion-like proteins.

It is possible that the altered transthyretin makes vitamin A less available to cells. Vitamin A deficiency creates major disruption of the framework proteins. Fragments of starch molecules inhibit the enzymes that remove inappropriately bound sugar molecules from proteins, and the inability to metabolize sugar into carbon dioxide increases that binding. Starches and unsaturated fats cooperate in this process of inappropriate sugar binding, while thyroid hormone, and the carbon dioxide it produces, tend to prevent the binding.

Considering the universal importance of carbon dioxide to life, the ways it interacts with all of the important substances that make up organisms, that it is involved closely with ATP synthesis and other "energy-related" processes, that it participates intimately in the regulation of water and ions, that it is therapeutic in a range of conditions including angina pectoris, hypoxia, epilepsy, inflammation, shock, lipid peroxidation, pneumonia, and asthma, I think we can at least conclude that it is a largely overlooked mediator between chemical energy and life processes. In many cases, its movements and reactions constitute the actual motive force that so many fantasy theories have failed to explain. In other situations, it fills out the context for understanding the energy-mediating actions of ATP, calcium, and hormones.

In the special arrangement of matter that is the living state, in which the most common events involve processes that are so close to equilibrium that some of them can be thought of as oscillations in an elastic system, carbon dioxide participates in both enzymic and nonenzymic reactions that produce, conserve, transfer, and transform energy. In its quickly reversible binding to protein amino groups, for example, it alters the protein's electrical charge, its folding, and its manner of associating with water and other substances. Its availablility to occupy these groups protects them from attack by substances that would degrade the organism's energy and structure. If the protein, water, ionic system

is thought of as energized matter, like a wound-up watch spring, it is the formation of carbon dioxide which has energized it and stabilized it.

Energy and Structure in Biological Water

A New Approach to Aging, Metabolic Inefficiency and Cancer

Energy and Character, Volume 4, Number 3, 1973

Biochemistry and even biophysics tend to be ruled by an emphasis on structure, at the expense of energy or function. The popular unit of biological energy is the chemical bond energy of ATP, a concept which has been notoriously unproductive in attempts to understand biological energy transformations such as nerve and muscle function, amoeboid movement, cell division, etc. That molecular concept of energy, despite its popularity, is derived from chemical equilibrium studies, and is not really applicable to the non-equilibrium, "steady state" conditions of life.[1] The study of biological energy transmission, transduction, and integration have been shunned, in favour of static models—for example, a famous researcher in "cell motility" has spent thirteen years manipulating wooden blocks representing molecular structures. Nevertheless, there is now enough information on the physics of macromolecules, water, and electrons and their interactions to support some very detailed interpretations of biological functions, including such well known, but hard to understand, interactions as memory and molecules, hormones and desires, emotions and cancer, loss of curiosity and aging, etc.

Prolonged discharge or activation of a cell tends to consume the molecular reservoir of energy, to "lower the energy charge" of the cell. Various physical measurements suggest that this is accompanied by an actual "melting" of the protoplasm. "Melting" does not necessarily mean going from hard to soft, and doesn't require changes in temperature. The general meaning of the concept as it is used here is "a phase transition from relative order to relative disorder." Glass, though very hard, is considered not to be a true solid because of its molecules' random arrangement. Likewise, fluid water can have different degrees of internal order, or structure, depending on its temperature,[2] its "history"[3] (its state during the last several hours) and its distance from a surface.[2] The proton, or hydrogen, component of the water molecule aligns itself with an electromagnetic beam, and so the freedom of water molecules can be measured by determining the nature of its absorption at certain frequencies. Such measurements have revealed that the water in tissue

is more highly ordered than ordinary water, and that cancer[4] and fetal[5] tissue and other new growth contain more water but their water is more like ordinary water, or more "melted."

In the presence of oil, or any unwettable surface, water becomes immobilized and ordered; conversely, ordered water will admit oily molecules more readily. Hydrophilic chemicals, such as sugar, will dissolve more easily in ordinary or relatively "melted" water: cancer cells are known to take up more glucose than normal cells do; insulin probably has a similar effect (a melting of the general protoplasm, follows insulin treatment).

Otto Warburg[6] related what he called "structure" to the ability of cells to use oxygen and to the ability of tissue to differentiate. He believed that evolution to the multicell stage depended on the existence of atmospheric oxygen. For several decades he gathered evidence to support his theory that cancer resulted from damaged respiration. However, his concept of "structure" was limited to such cellular components as the mitochondrion.[7] His general theory has withstood every challenge over the last thirty years.

If the cancer process represents a self-stabilizing reversal of evolution to the single cell stage, it can also be considered as a reversal of ontogenesis to a very early stage of embryonic development. Several theories have been based on the similarities of cancer to the early embryo (metastasis, non-allergenic proteins).

At the blastula stage of development, the embryo suddenly begins to consume large amounts of oxygen. As oxygen consumption increases, the water content decreases,[8] so that what remains is increasingly "surface" dominated, that is, on the average it is closer to macromolecules. Therefore, it must be more highly structured. The excited electronic state of oxygen is stabilized by cell water, just as the excited state of many fluorescent molecules is stabilized by ice, but not by ordinary water. This stabilization of the excited state could facilitate oxidation. Stabilization tends to be mutual; if this is the case, then oxidation might support structure in the water.

The fact that structured water promotes protonic conduction as well as prolonged electronic excitation should extend the range of molecular interaction, possibly even to the extent of intercellular adhesion. This would provide an explanation for cancer cells' loss of adhesiveness which results in secondary cancer growths. Resonant stabilization of one cell by

another would similarly account for the "contact inhibition" of normal cells. In the "melted" state cells would be limited to the less efficient anaerobic metabolism, because of the altered solubility and stabilization of oxygen, but they would maintain the primitive function of growth. If hydrostatic pressure can be considered to interfere with cell water structure,† this view would predict the observation of Chumak[9] that high pressure shifts the metabolism of bacteria from oxidation to fermentation. However, very high pressures can also interrupt cell division; growth under such conditions can lead to very long cells.

Free electrons in water will stabilize themselves by forming cages of water molecules around themselves, because of the electrically polar nature of water molecules. They are known to be much more stable in ice than in liquid water, and might be similarly stable in cell water. These electrons in solution have a deep blue colour, and are probably responsible for the blue colour of water and ice, which becomes much more intense at high elevations where free electrons are more abundant. If the structure of water in healthy cells is such that it would stabilize solvated electrons, then an abundance of free electrons should tend to stabilize the normal structure of cell water.

These concepts provide a new perspective in which to consider brain function and other processes in which pattern is essential, including tissue development. Instead of a computer with neuronal "wires," the brain can be viewed as a living jelly, in which nerves might have only a nutritive and transport function, with information storage and retrieval and consciousness in general being a hologram-like function of patterned flows of electrons through a very finely structured protein-polysaccharide-lipid-water gel. In this model, an act of consciousness (a structured flow) is simultaneously retrieval and storage, since structure will be modified or intensified according to the form of the flow, yet the flow will also be governed by the structure. Growth of generalized insight is synergic with intensity of experience, according to this model. This simple conception, derived from physical and metabolic studies,[10] is able to explain complex integration and message transduction, but its most outstanding advantage over the computer model is its ability to explain the experience of time in terms of an energy gradient which

† *cf.* The effects of stasis on the body fluids in Reich's account of cancer.

is known to exist (measured as a positive charge of the anterodorsal surface) and to correlate with changes in subjective states.

Palladin,[11] who demonstrated that innervation governs enzyme activity, has more recently found that efficient use of oxygen for energy production by brain tissue increases with evolutionary level (in reptiles, birds, and mammals) and with the degree of alertness. Level of brain activity and local innervation have been found to be involved in tumor growth,[12] and in the ability of tissue to form a reactive inflammation. These themes of enzyme activity changes and efficiency of oxidative metabolism, which are so important to the problems of evolution, consciousness, growth, and cancer, can be seen in the perspective of water structure with very surprising results.

Certain enzymes are inactivated by cold, and reactivated by moderate warmth; other enzymes are activated by the presence of molecules known to structure water, and inactivated by structure breakers, such as the fluoride ion. The enzymes which are activated by the relative disorder of warm water happen to be the enzymes which control a pathway of energy metabolism which becomes active in the growth state. Estrogen, chemical carcinogens, radiation, and lack of oxygen are known to activate this pathway. Normally, the energy produced by these reactions provides for regeneration following injury. Nerves, hormones, physical structures, and oxygen normally intervene and restore the high energy metabolic system necessary for differentiated functioning. If any of these factors is inadequate, the new tissue can stabilize into cancer, with its own "toxohormone," its own peculiar physical environment of abnormal connective tissue, and its own system for "wasting" oxygen,[13] all of which maintain the "melted" state of protoplasm with its primitive metabolic pathways. The other enzymes that are activated by structure, tend to be implicated in the high energy processes, and may suggest new approaches to the treatment of cancer.

Burr,[14] and more recently Becker,[15] have found that organ development is governed by an electric charge gradient in the organism. This gradient declines with age. Individual cells drift toward the inefficient oxygen wasting mode of metabolism with increasing age. Tissue electrical resistance increases with age. Accumulation of material between cells and disorganization of cell water probably contribute to the poor conductivity. It is possible that the high concentration of free electrons at high elevations increases the life span by helping to maintain the

high efficiency cell structure. (Vitamin C, a source of fairly high energy electrons, is known to support normal fetal development, even in the presence of powerful drugs which act by blocking respiration.)

Time-spanning is essential to consciousness; insightful perception seems to depend on the ability to directly perceive patterns that extend through time. Time is needed for consciousness to complexify, to have insights. But eventually, this growth function of time is directly subverted by another function of time, which insulates, lowers energy, shortens the time span of perception, and causes tissue degeneration. Possibly the simple interactions of electrons and water, energy and structure, will suggest new approaches to the treatment of senescence and associated diseases.

Estrogen Stimulated Pathway Changes and Cold-Inactivated Enzymes

Physiological Chemistry and Physics, Volume 4, April, 1972

It is well established that water near surfaces, including macromolecules and biological material, is very different from bulk water,[1] although the degree of ordering and the distance to which an effect is exerted are still in dispute. Shereshefsky,[2] Bernal,[3] Derjaguin,[4] Drost-Hansen[1] and others[5] have argued for an effect of surfaces on water structure at distances up to hundreds of Angstroms, or even farther. NMR studies have shown that tissue water is more restricted than bulk water, and that the water in young[6] or actively dividing tissue such as cancer[7] (which contains a higher than normal percentage of water) is more "bulk-like" than the water of more mature and stable tissue.

Temperature anomalies of enzyme activity have been attributed to solvent effects as water undergoes minor phase changes.[1] Cold-inactivation and cold-activation of certain enzymes probably represent extreme cases of such "anomalous" behavior, and at least for enzymes with more than one subunit, can be accounted for by the fact that hydrophobic bonds tend to be weakened by decreasing temperature.[† 89, p. 7010]

In an earlier paper,[11] we suggested that estrogen may act through an effect on the energy charge and the water structure of uterine cells, and that this very general effect may explain why various non-specific insults (e.g., radiation,[12] possibly hypoxia,[13] and diverse substances such as carcinogens[14] and histamine[15, p. 265]) have an estrogenic effect. Even age may have an effect similar to estrogen.[16–18]

It has recently been brought to our attention (A. R. Larrabee, personal communication) that fatty acid synthetase is cold-inactivated, and also that its activity in rat liver drops very sharply as early as two hours after feeding is stopped. This inactivation by cold has been attributed to dissociation resulting from weakening of hydrophobic bonds at low temperature.[19] Since lipid is the first substance to increase greatly in concentration in the estrogen activated uterus (although other compo-

[†] "…remember that thermal energy [kT] tends to disorder structures and, conversely, a lowering in temperature will increase the ordering."[1, p. 186]

nents show very early incorporation of label following estrogen stimulation[20, p. 1]), this fact is extremely interesting in relation to our proposal that estrogen increases the "structural temperature" of cell water, and so would tend to activate the cold-inactivated enzymes.

The other cold-inactivated enzymes from various organisms and tissues include pyruvate kinase,[21] glutamate dehydrogenase, ATPase, arginosuccinase, glycogen phosphorylase, pyruvate carboxylase, glucose-6-phosphate dehydrogenase, 17β-hydroxysteroid dehydrogenase,[8] acetyl CoA carboxylase,[22, p. 304] and the "muscle" or electrophoretically slow moving isozyme of lactic dehydrogenase,[23,24] which would also be suitable for regulating pathway changes involved in cellular activation. For example, phosphorylase activity is promoted by estrogen treatment.[25] Glycogen breakdown can be rate-limiting for glycolysis.[26, p. 572]

Estrogen stimulation, hypoxia, and carcinogenesis involve an increased proportion of the "muscle" isozyme of lactic dehydrogenase, which represents a useful adaptation to a glycolytic production of pyruvate that is larger than can be oxidized by the mitochondria or otherwise disposed of, since this isozyme can continue to oxidize NADH and reduce pyruvate even in the presence of high concentrations of pyruvate.[27]

Entropic activation of pyruvate carboxylase could tend to increase fixation of carbon dioxide[28] and production of oxaloacetate, which by transamination would increase aspartate concentration. According to Jervell et al.[29] the labeled aspartate pool (from $H^{14}CO_3$) is increased by estrogen to a greater extent than that of glutamate, suggesting that it, and its α-keto acid, oxaloacetate, are near the point of CO_2 fixation.

Barker and Warren[30] showed that the glucose-6-phosphate oxidation pathway is immediately activated by estrogen, yet the specific activity of glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase decreased for the first six hours. Activation of these enzymes and raising of the NADP/NADPH ratio by the estrogen activated transhydrogenase, or by lactic dehydrogenase,[31] and even CO_2 fixation could contribute to the acceleration of this process.

It has been found that estrogen binding capacity of the uterine "receptor" molecule is considerably reduced at low temperature, and that the binding capacity is restored by raising the temperature,[20, p. 1] and Talwar et al.[32] reported that the rate of binding of estrogen to a soluble uterine fraction increases with incubation time as well as with temperature, indicating a kind of cooperative interaction. It has been proposed that

this change of binding might represent a temperature dependent transfer to the nuclear receptor, but Talwar's use of a "purified" extract argues against this view. The data relating to temperature effects on binding are consistent with the idea of a phase shift promoted by estrogen. Ling[33] has reported that progesterone increases the potassium selectivity of myometrium. Cone and Tongier[34] and Orr et al.[35] have found that the Na^+/K^+ ratio can very rapidly affect mitosis and DNA synthesis. Mueller et al.[36] observed that incubation in Eagle's medium can mimic estrogen stimulation. Such considerations suggest that it might be worthwhile to study the receptor protein as a possible initiator of phase transition, as an alternative to the view that it primarily serves to transfer estrogen to the nucleus.

Engel[37] has reported that one of his estrogen activated transhydrogenases has an affinity and specificity for estrogen comparable to that of the "receptor" protein, although the 17β-estradiol dehydrogenase has a lower affinity. If an intracellular enzyme binds estrogen and has its function modified by it, it is a receptor, but there is no evidence that the well known "9 S" receptor has enzyme activity. One of the seemingly well established "coenzyme" functions of estrogen is in the estrogen activated NADH oxidase function of peroxidase.[38] Peroxidase is "induced" in the uterus by estrogen treatment.[39]

Temple et al.[40] found that the oxidase behaved "like an induced enzyme," except that "oxidase activity was stimulated by the administration of estradiol to oophorectomized rats in two hours, when net protein synthesis cannot be detected." "Receptor" protein is also "induced" by estrogen.[41,42] Whatever the relation of "receptor" to estrogen activated enzymes might be, the apparent oxygen wasting effect of the estrogen activated oxidase would help account for estrogen's ability to lower the Pasteur effect[43, p. 348] and to lower the pO_2 of the uterine lumen,[44] and this effect would be compatible with the above mentioned diversion of pyruvate to oxaloacetate (which would tend to inhibit succinic dehydrogenase) and with the shift[44] toward M isozymes of LDH, which appears to correspond to hypoxia and would also divert pyruvate from oxidation. A consequent reduction of the energy charge might cause the phase change, or damage to structure as suggested by Warburg.[45, p. 327] Racker[46] has recently proposed that increased temperature or altered pH may be involved in activation of the glycolytic pathway in cancer, and suggests increased hydrolysis of ATP as a possible cause. It was Racker

who first observed that mitochondrial ATPase is cold-inactivated, and he has also pointed out that damage to mitochondria can reveal very high levels of ATPase activity.

Other physiological processes that might be accounted for by an entropic modification of protein association and enzyme activity include:

(a) ammonia formation by stimulated nerve,[47] muscle,[48] and uterus,[†] since glutamate dehydrogenase is among the known cold-inactivated enzymes and these tissues[‡ 49,50] seem to undergo a water phase change when stimulated;

(b) estrogen stimulation of water uptake, by a thermo-molecular pressure effect,[51] because of increased metabolic rate[52] and possible change of heat conductivity,[1] or by a more direct effect on gel structure;

(c) estrogen's effect of increasing ATPase activity of the uterus,[53] which might relate to the increased myometrial reactivity in the estrogen dominated uterus;

(d) microtubule formation, since these seem to be cold sensitive;[54] also, H. Nemetschek-Gansler,[55, p. 353] in describing the ultrastructure of the myometrium under the influence of estrogen says that the appearance "suggests a high degree of depolymerization of the contractile proteins," and that progesterone produces something like syneresis, implying altered protein-water interaction;

(e) vernalization.[1] This is a process involving an actual and large temperature difference rather than merely a structural difference. Cold-activation of enzymes would be the expected mechanism.

Abdulla and McFarlane[56] suggest that since a pyrophosphatase is activated or "induced" on the surface of platelets by collagen, and inhibited by NaF, this enzyme may belong to a class of enzymes activated by solvent structure. It has been proposed that association in some cases blocks active sites. In such cases increased solvent structure would increase activity or lower substrate specificity, if it weakened hydrophobic bonds.

[†] Inferred from observations in this laboratory.
[‡] NMR studies currently being done in this laboratory.

(Xanthine oxidate is well known as a cold-activated enzyme,[57] possibly involving such a mechanism.) Since pyrophosphatases are involved in establishing equilibria favorable to synthesis of protein (amino acid activation), RNA, and DNA, and oxidation of fatty acids, the concept of activation by solvent structure would imply that these processes belong to a later period in cell activation, in which a certain degree of order has been restored. The known schedule of syntheses following estrogen stimulation is consistent with this view. Either androgen or progesterone, which can increase metabolic "efficiency,"[58] would probably be involved at this stage. Progesterone's thermogenic[28] and anesthetic[59] effects seem significant in this context. A theory recently proposed[60–62] for control of enzyme levels could account for apparent induction or repression by cytoplasmic stabilization of some proteins, and by destabilization of others.

This entropic and energetic interpretation presents dedifferentiation as a simple, stable, and general change of state. Differentiation remains as a highly individualized process, depending on a precise history and environment of each cell. However, the simplicity of this view of dedifferentiation suggests a relatively small number of points at which effective intervention might be made in altering the course of carcinogenesis. It also suggests possible new approaches to fertility, sterility, and aging.

Estrogen in 1990

Townsend Letter for Doctors, April 1991

The Magic of Estrogen Therapy

A stage magician can produce surprising illusions by directing the audience's attention to where something is not happening, or to a distracting gesture. The billion-dollar estrogen industry has learned the trick of directing the public's attention to where some plausible benefit might be expected, and of politely ignoring the areas where death and destruction are in fact being produced.

Interestingly, another billion-dollar industry—the edible oil industry—is using the same prestidigitation to profitably misinform the public. Decades ago, unsaturated oils were found to lower cholesterol. However, studies showed that adding the polyunsaturated oils to the diet didn't prevent death from heart disease, but that it did increase cancer deaths. There were also warnings that the oils could cause problems with blood clotting. There was silence from the industry, the government, and the medical profession in response to the bad news.

When evidence of an association between blood lipids and heart disease was found, the blood tests, rather than actual health, became the focus of publicity. A high ratio of HDL (high density lipoprotein) to LDL (low density lipoprotein) came to be identified with "health," because of its association with lower risk of heart disease, although it was also an indicator of a risk of death from cancer. By ignoring everything but heart disease, it could be argued that "If high HDL equals health, and estrogen and PUFA (polyunsaturated fatty acids) cause HDL to increase, then these things promote health."

Concerning estrogen, similarly twisted reasoning led to its trial in the 1960s to prevent heart attacks in men, but the experiment was stopped when the rate of heart attacks increased sharply.

Focus on the positive. Ignore the HDL-cancer association. Ignore the association of estrogen with thrombosis, embolism, stroke, edema, obesity, depression, myocardial infarction, eclampsia, epilepsy, brain damage, and immunodeficiency. Ignore the implications of thyroid suppression.

In her comedy routine, Judy Tenuta describes a most implausible situation, and then belligerently pleads: "It could happen; it could happen." The ignorance or mendacity which allows experts to plead the importance of one possible benefit, in the face of clear evidence of a multitude of serious dangers, defies any sort of conventional scientific response.

The recent corruption scandal involving the FDA's generic drug division might come to mind when I suggest that Tenuta's satire illuminates the attitude of the FDA (and the medical industry), but I believe the indictments are part of the prestidigitation. Marvin Seife, who was head of the generic drug division, was indicted for perjury. The indicated intent of Congress had been to support generic drugs to break the monopoly of the biggest drug companies; but for the last six years there has been an intense campaign by the monopolies to keep generic drugs off the market, and Seife's indictment must be evaluated in this context.

Earlier, an FDA official who was too friendly toward DMSO and its developer, Dr. Jacob, was exposed for accepting a loan from the doctor. While keeping new entrepreneurs from intruding into the fabulously lucrative drug business, those little prosecutions allow the public to believe that the government is policing itself. (If your corporation could expect an additional $4,000,000,000 in profits in the next 10 years, but only if a few men would narrow the scope of their judgment, how do you suppose you could encourage those few men to go in the right direction?)

Just One Problem: Clots

Forty-five years ago the Shutes found that estrogen promotes the clotting of blood. At the same time, Knisely was studying the phenomenon of "blood sludging," which occurs under many types of stress. At that time it was recognized that there is an equilibrium between clot formation and clot removal (fibrinolysis).

Vitamin E and magnesium and some substances produced by the body shift the balance away from clots. Estrogen, calcium, altered water content and blood volume, and sluggish flow of blood encourage the formation of clots. Some contemporary articles acknowledge that estrogen can cause thrombophlebitis or thromboembolism and can exacerbate

gallbladder and liver disease and breast cancer, but these warnings are subordinated to praising the benefits of estrogen replacement therapy.[1]

Some quotations from the ERT article by Miller, et al.,[1] illustrate current medical attitudes.

"Although the reasons for its apparent protective effect on the heart are not fully understood, oral estrogen does decrease low-density lipoprotein cholesterol and increase high-density lipoprotein cholesterol."

"Although no prospective study has yet shown that estrogen protects against cardiovascular disease, other studies show that women who use estrogen or who have ever used estrogen have a reduced risk of heart disease. The only study that has not confirmed these results is the Framingham Heart Study, which contained smaller numbers of older women and classified chest pain—a notoriously poor identifier of heart disease in women—as a cardiovascular end point." (p. 47)

The prospective long-term Framingham study noted above used to be highly praised as a source of reliable information on heart disease. In contrast, some of the studies that are praised in prestigious journals are wildly unscientific. For example, the heart disease in Marin County women receiving estrogen has been compared with that of women in the East Bay not getting estrogen. Marin County is a rich residential area, which is swept by ocean breezes while across the bay there are more working class people (and working class men are known to have nearly 50 % more heart disease than white collar workers), and the wind from one direction blows smoke from a concentration of industries and refineries, from another direction it carries the pollution from San Francisco's traffic, and from another direction it brings the agricultural poisons of the Salinas area.

If enough women die from strokes, pulmonary embolisms, accidents, suicide, cancer, and loss of immunity caused by estrogen excess, it is possible that some competent study will eventually show that estrogen treatment reduces the mortality from heart attacks, but this is not likely.

It is the estrogen in oral contraceptives which correlates with their effects on the clotting system. In the last 20 years there has been general agreement that increased risk of cardiovascular disease, rather than cancer or immunodeficiency or depression, is the most important concern about the effects of oral contraceptives.[2–12]

There are many ways that estrogen can contribute to a hypercoagulable state (leading to cardiovascular disease). Some of these involve

altered liver function, including disturbed production or metabolism of 8 different coagulation controlling factors.[13,14] Since estrogen can stimulate endothelial proliferation (often cited as crucial in heart disease) and reduces the rate of venous flow,[15,16] it is necessary to consider the whole complex circulatory system, and not just the clotting factors.

The thyroid and other hormones such as insulin and adrenalin are influenced by estrogen, and must be taken into account. Although I'm not sure what clinical perceptions led the Shutes to study estrogen's affect on clotting, pregnancy and lactation are notoriously associated with hypercoagulability (eclampsia and thromboembolism, for example) produced by the body's high estrogen production at those times.[17–24] The very high doses of estrogen that were once used to suppress lactation were found to produce clotting problems.[25] Postmenopausal use of estrogen causes changes in coagulability.[13,14,26]

In the mid-1970's when I pointed out that menopause resembles Cushing's syndrome[27] I hadn't investigated that disease of cortisol-excess enough to know the full extent of the parallel: for example, hot flushes, night sweats, and insomnia, such common menopausal symptoms, are also common symptoms in Cushing's syndrome. Estrogen's tendency to increase cortisol production should be considered in connection with the brain-aging effects of both estrogen and cortisol.[28,29]

Both estrogen and cortisol weaken the structural components of tissue, and the bruising which is so commonly associated with the premenstrual syndrome seems to involve the unopposed action of both of these hormones. The women who often have bruised thighs in their twenties are later susceptible to hemorrhages into the white part of the eye, and still later to bleeding into the brain, presumably because there is a hierarchy of protection against the tissue-weakening effects of those hormones, with the brain being the last to lose its resistance.

For example, the brain content of progesterone, pregnenolone and DHEA is normally 20 or 30 times higher than the serum concentration, and these hormones are protective against both estrogen and cortisone. As far as I know, it is possible to have fragile blood vessels at the same time as an excessive tendency to clot, though when the vessels break, the extent of the bleeding will be smaller in the hypercoagulable state. The observation that low cholesterol is associated with increased risk of hemorrhagic stroke[30] suggests that the age-related decline in progesterone,

pregnenolone, and DHEA occurs earlier when there is a low level of the precursor substance, cholesterol.

Clotting too easily is just one of the problems that can be caused by an excess of estrogen, and I don't mean to give it too much emphasis, since I consider its toxic effects on the brain, and its acceleration of brain aging to be its worst effects—though its cancer inducing effects on the uterus, the breast, the lung, the bowel and liver, and brain, are certainly serious. But in 1990, estrogen's cardiovascular toxicity is probably the aspect that people need to be reminded of.

Failures of Immunity

Townsend Letter for Doctors, December, 1992

FROM ancient times until the 1940s, young adulthood was the healthiest phase of life, with an insignificant rate of death from disease. Septicemia, bacterial infection in the blood, had been associated with the natural immune deficiency of old age. By the 1960s septicemia was killing many young adults, in spite of the susceptibility of the germs to antibiotics.[1,2] The use of antibiotics did save enough immune deficient people from septicemia to allow an increasing incidence of other diseases, including *Pneumocystis carinii* pneumonia, to become apparent. Acquired immune deficiency (AIDS) was a recognized syndrome for many years, and it was known to be increasing long before the 1980s.[3]

P. H. Duesberg had made the point that most of the present AIDS epidemic can be explained by the various known causes other than the HIV virus. I think he is mostly right, but I don't exclude the possibility that the virus in itself could be a significant cause of the disease. My judgement would be that the virus is a "co-factor" in the disease, and by this I mean that we have been exposed to an increasing burden of immunosuppressive factors, which are causing an exponentially rising curve of immunodeficiency diseases, and that, arriving at a certain point on that curve, the HIV virus would help to push the rate of increase upward.

Besides the generally increasing industrialization and pollution, in the 1950s there were sudden increases in our exposure to several powerfully immunosuppressive factors. Radioactive fallout (especially strontium 90, which concentrated its damage near the bone marrow), medical X-rays, dioxins and other chlorinated carbon compounds, insecticides and herbicides, the increased promotion of the use of liquid vegetable oils as food, and the use of lead as a gasoline additive, had all become important immunosuppressive factors by 1960. The relative importance of these varied with the person's age, vocation, customary diet, social class, etc. For example, rich people were more likely to have prenatal X-rays, and poor people were more likely to have lindane applied to their skin to kill lice.

A low level of the hormone DHEA is associated with premature death from various causes, including cancer, heart disease, and AIDS.

DHEA is one of the youth-associated, energy-promoting, anesthetic steroids which I have described as essential to our natural resistance. (For example, in *Natural Immunity and Viral Infections*, I said "Pregnenolone, progesterone, DHEA, and pregnanediol are all good candidates as antiviral drugs, but etiocholanolone—which also produces fever—is the most interesting of the group.") In general, the things that lower vitality and immunity interfere with our ability to produce the protective steroids.

Those hormones are made from cholesterol, and both low and high concentrations of blood cholesterol are associated with immune defects. Most of the people I have talked to who have multiple serious allergies have very low cholesterol levels, and hypothyroid people who are very susceptible to infections usually have high cholesterol, and in both situations there isn't adequate production of hormones from cholesterol.

Often, the idea of "auto-immune disease" serves as an excuse for the use of immunosuppressive treatments, such as glucocorticoids or methotrexate, so I usually avoid the word and the concept. Antibodies against specific tissues are probably part of a normal process to take care of damaged cells. For example, simply twisting a piece of cartilage makes it antigenic. After talking to many people who had anti-thyroid antibodies which disappeared soon after their thyroids became normal from physiological therapies, I decided that "auto-immune" antibodies were useful to indicate which organ was under stress, but shouldn't be taken as a sign of an "immunological disease." Still, the immune system, like any system, can become ineffective or sick, and it is possible that a sick immune system could make some problems worse. (I have previously used the analogy of an "allergy" to discuss this view of AIDS.)

Morphine has been known to be immunosuppressive for several decades, though this fact has been ignored in prescribing it for cancer patients. (Intravenous ethanol has a protective effect on the immune system, and is as effective as morphine in controlling the pain of cancer.) Morphine's directly suppressive effect on immunity isn't understood, but there is some suspicion that it relates to the stress-induced immunosuppression (loss of natural killer cell function, for example), acting in place of stress-induced endorphins. White blood cells, like nerve cells, have surface "receptors" for morphine, which normally would be acted on by the endorphins. As an abnormal material bound to the cell surface, it probably constitutes a "hapten," something sensed by other white

blood cells as foreign. It would be healthy to eliminate such abnormally modified cells, and even possibly to eliminate the cells that contain the natural endorphin molecule. But in a weakened organism, the formation of new cells might lag behind the elimination of modified cells.

Deusberg has said that it seems illogical that a person should get sick, just as he is beginning to produce large numbers of antibodies to the HIV virus, but it wouldn't be illogical if the antibodies were eliminating cells faster than they could be replaced. His point, that only one cell in 100 carrying the virus isn't enough to cause failure of the immune system, is true, other things being normal. But an allergy can be triggered by very small quantities of allergen. In a failing immune system, a few molecules of morphine or a few viral antigens could be enough to trigger a kind of autoimmune/allergic response, which could cause a massive suppression or disorganization of immune function.

But even if such a thing is involved in AIDS—even if the HIV virus is a true cause of AIDS—Duesberg is right in emphasizing that we have to think of immune deficiency in a broader context, of eliminating all the immunosuppressive factors, and understanding the real nature of the immune system.

If antibodies turn out to be part of the problem, we shouldn't think of searching for additional immunosuppressive drugs, because we already know of situations in which antibody production increases while immunity is being impaired, as if in compensation for a weakness in cell-mediated immunity. Increasing the production of the cells that are deficient and improving their functioning, should be the focus of attention. The increased incidence of septicemia among young adults suggests that phagocytosis was deficient. Since Metchnikoff's time there hasn't been much interest in the phagocytes, but I think that is beginning to change.

Folic acid is so important for proliferation and differentiation that I think it's worthwhile to take about 5 mg daily for a week or two.

Vitamin A is important for resistance, but carotene can interfere with retinol.

Carotenemia suggests a lack of vitamin B_{12} or thyroid, and interferes with thyroid and steroid production.

Another thought: if you ate vegetables, whole grains and legumes in the 1960s, your bones are rich in strontium 90. Vigorous osteoclasts are working to get rid of it, by phagocytosis. Warm bones are young bones.

Gas Industry's "Shortage"

Science News, Volume 102, Number 12, September, 1972

PEOPLE who express confusion about the gas industry's story of short supplies and their search for new ways to increase consumption of gas, should read Robert Sherrill's "Energy Crisis! The Industry's Fright Campaign," in the June 26 *Nation*. He points out that in 1968 the U.S. Supreme Court rejected higher profits on gas because "each year new reserves exceeded production." Then "beginning in 1968, and for the first time in history, the industry claimed that it found less gas than it sold. It has been claiming the same thing for every year since. The basis for these claims is in industry's file cabinets, secret, not available to Congress or to the public."

An interesting contrast to this situation is that in the U.S.S.R., where energy is publicly owned, there is serious scientific discussion of the possibility that natural gas might be truly inexhaustible, as a result of continuous replacement in a natural energy cycle.

There is a similar contrast in our attitudes toward the fixation of atmospheric nitrogen by higher animals: The Russians have studied it for many years, while all but a few American scientists ridiculed the notion, preferring to talk about the "world protein crisis" and population control.

Hormone Balancing: Natural Treatment and Cure for Arthritis

The Journal of the Rheumatoid Disease Foundation, Volume 1, Number 1, 1986

A very healthy 71-year-old man was under his house repairing the foundation, when a support slipped and let the house fall far enough to break some facial bones. During his recovery, he developed inflammatory arthritis in his hands. It is fairly common for arthritis to appear shortly after an accident, a shock, or surgery, and Hans Selye's famous work with rats shows that when stress exhausts the adrenal glands (so they are unable to produce normal amounts of cortisone and related steroid hormones), osteoarthritis and other "degenerative" diseases are likely to develop. But when this man went to his doctor to "get something for his arthritis," he was annoyed that the doctor insisted on giving him a complete physical exam, and wouldn't give him a shot of cortisone. The laboratory examination showed low thyroid function, and the doctor prescribed a supplement of thyroid extract, explaining that arthritis is one of the many symptoms of hypothyroidism. The patient agreed to take the thyroid, but for several days he grumbled about the doctor "fixing something that wasn't wrong" with him, and ignoring his arthritis.

But in less than two weeks, the arthritis had entirely disappeared. He lived to be 88, but without a recurrence of arthritis.

Selye's work with the diseases of stress, and the anti-stress hormones of the adrenal cortex, helped many scientists to think more clearly about the interaction of the organism with its environment, but it has led others to focus too narrowly on hormones of the adrenal cortex (such as cortisol and cortisone), and to forget the older knowledge about natural resistance. There are probably only a few physicians now practicing who would remember to check for hypothyroidism in an arthritis patient, or in other stress-related conditions. Hypothyroidism is a common cause of adrenal insufficiency, but it also has some direct effects on the joint tissues. In chronic hypothyroidism (myxedema and cretinism), knees and elbows are often bent abnormally.

By the 1930s, it was well established that the resistance of the organism depended on the energy produced by respiration under the influence of the thyroid gland, as well as on the adrenal hormones, and that the

hormones or pregnancy (especially progesterone) could substitute for the adrenal hormones. In a sense, the thyroid hormone is the basic anti-stress hormone, since it is required for the production of the adrenal and pregnancy hormones. A contemporary researcher, F. Z. Meerson,[1] is putting together a picture of the biological processes involved in adapting to stress, including energy production, nutrition, hormones, and changes in cell structure.

While one of Selye's earliest observations related gastro-intes tinal bleeding to stress, Meerson's work has revealed in a detailed way how the usually beneficial hormone of adaptation, cortisone, can cause so many other harmful effects when its action is too prolonged or too intense. Some of the harmful effects of the cortisone class of drugs (other than gastro-intestinal bleeding) are: Hypertension, Osteoporosis, delayed healing, atrophy of the skin, convulsions, cataracts, glaucoma, protruding eyes, psychic derangements, menstrual irregularities, and loss of immunity allowing infections or cancer to spread.

While normal thyroid function is required for the secretion of the adrenal hormones, the basic signal which causes cortisone to be formed is a drop in the blood glucose level. The increased energy requirement of any stress tends to cause the blood sugar to fall slightly, but hypothyroidism itself tends to depress blood sugar. The person with low thyroid function is more likely than a normal person to require cortisone to cope with a certain amount of stress. However, if large amounts of cortisone are produced for a long time, the toxic effects of the hormone begin to appear. According to Meerson, heart attacks are provoked and aggravated by cortisone produced during stress. (Meerson and his colleagues have demonstrated that the progress of a heart attack can be halted by a treatment including natural substances such as vitamin E and magnesium.)

While hypothyroidism makes the body require more cortisone to sustain blood sugar and energy production, it also limits the ability to produce cortisone, so in some cases stress produces symptoms resulting from a deficiency of cortisone, including various forms of arthritis and more generalized types of chronic inflammation. Since cortisol is formed as one of the last steps in a series of reactions, glandular exhaustion means that a whole group of other steroids is depleted, before cortisol or cortisone. I believe that the safest way to handle a steroid deficiency is to supplement the precursors of the raw materials, so that a normal balance

of the various substances is preserved. Often, a small physiological dose of natural hydrocortisone can help the patient meet the stress, without causing harmful side effects.

While treating the symptoms with cortisone for a short time, it is important to try to learn the basic cause of the problem, by checking for hypothyroidism, vitamin A deficiency, protein deficiency, a lack of sunlight, etc. (I suspect that ultraviolet light on the skin directly increases the skin's production of steroids, without depending on other organs.) Using cortisone physiologically, rather than pharmacologically, it is not likely to cause the serious problems mentioned above.

Stress-induced cortisone deficiency is thought to be a factor in a great variety of unpleasant conditions, from allergies to ulcerative colitis, and in some forms of arthritis. The stress which can cause a cortisone deficiency is even more likely to disturb formation of progesterone and thyroid hormone, so the fact that cortisone can relieve symptoms does not mean that it has corrected the problem.

Besides the thyroid, the other class of adaptive hormones which are often out of balance in the diseases of stress, is the group of hormones produced mainly by the gonads: the "reproductive hormones." During pregnancy, these hormones serve to protect the developing baby from the stresses suffered by the mother, but the same hormones function as a part of the protective anti-stress system in the non-pregnant individual, though as a lower level.

Some forms of arthritis are known to improve or even to disappear during pregnancy. As mentioned above, the hormones of pregnancy can make up for a lack of adrenal cortex hormones. During a healthy pregnancy, many hormones are present in increased amounts, including the thyroid hormones. Progesterone, which is the most abundant hormone of pregnancy, has both anti-inflammatory and anesthetic actions, which would be of obvious benefit in arthritis.

There are other naturally anesthetic hormones which are increased during pregnancy, including DHEA, which is being studied for its anti-aging, anti-cancer, and anti-obesity effects. (One of the reasons that is frequently given for the fact that this hormone hasn't been studied more widely is that, as a natural substance, it has not been monopolized by a drug patent, and so no drug company has been willing to invest money in studying its medical uses.) These hormones also have the ability to

control cell division, which would be important in forms of arthritis that involve invasive tissue growth.

While these substances, so abundant in pregnancy, have the ability to substitute for cortisone, they can also be used by the adrenal glands to produce cortisol and related hormones. But probably the most surprising property of these natural steroids is that they protect against the toxic side-effects of excessive adrenal hormones. And they seem to have no side-effects of their own; after fifty years of medical use, no toxic side effects have been found for progesterone or pregnenolone. Pregnenolone is the material the body uses to form either progesterone or DHEA. Others, including DHEA, haven't been studied for so long, but the high levels which are normally present in healthy people would suggest that replacement doses, to restore those normal levels, would not be likely to produce toxic side effects. And, considering the terrible side effects of the drugs that are now widely used, these drugs would be justifiable simply to prevent some of the toxic effects of conventional treatment. It takes a new way of thinking to understand that these protective substances protect against an excess of the adrenal steroids, as well as making up for a deficiency. Several of these natural hormones also have a protective action against various poisons—Selye called this their "catatoxic" effect. (If a toxin, for example a bacterial product, is involved in a sickness, such as arthritis or colitis, these catatoxic steroids might be helping by blocking the toxin and strengthening the patient.)

Besides many people whose arthritis improved with only thyroid supplementation, I have seen people use one or more of these other natural hormones for various types of arthritis, usually with a topical application, and I know of several other people who used progesterone topically for inflamed tendons or other inflammations. Only one of these, a woman with rheumatoid arthritis in many joints, had no significant improvement. An hour after she had applied it to her hands and feet, she enthusiastically reported that her ankle had stopped hurting. But after this, she said she had no noticeable improvement.

The first time I saw arthritis disappear after treatment with progesterone was accidental. A woman who began using progesterone for her epilepsy decided to dip her arthritic fingers in the oily solution, and a few days later proudly demonstrated that she could bend them without pain.

About a year later, a friend in Mexico City complained about a knee that had been increasingly stiff and painful for about a year. 20 min after applying progesterone the pain was gone, and when I asked him about it a few years later, he said it never hurt again. Knowing that those "raw material" steroids, pregnenolone, progesterone, and DHEA, could be converted into anything the body needs, such as cortisone and sex hormones, but that they protect against the toxic effects of other hormones, many other people (including physicians and researchers) were interested in trying them on their own joint problems.

Some typical cases are described below:

1. A 72-year-old woman. She was considered to have mild rheumatoid arthritis which was degenerating into porosis, with her fingers being the most seriously affected joints. A 3 % solution of DHEA in olive oil was applied to one index finger, and a 10 % solution of progesterone in mixed tocopherols was applied to the other index finger. All of her fingers had been rigid for over a year, with the result that she was extremely disabled. 40 min after the DHEA solution had been applied, the finger treated with that solution could be bent enough to touch the base of her thumb, without significant pain, but none of her other fingers showed any improvement. Several days later, the DHEA solution was applied to all of her fingers, with similarly good results. After about 6 months, stiffness and pain returned in spite of her use of DHEA. Although thyroid was suggested, she had been taught to be afraid of that hormone, as have millions of other women.

2. A 60-year-old woman with a long history of rheumatoid arthritis had serious degeneration of many joints. She had undergone surgery several times, for implantation of two artificial joints and for repair of joint cartilage. She walked a little as possible and experienced pain, inflammation and fatigue with excessive walking. She applied a solution containing 7 % DHEA and 3 % progesterone in a solvent consisting of olive oil and tocopherol. She applied the solution several times one afternoon and the next morning to all affected joints, including hands, wrists, elbows, knees, and ankles. She experienced what she said was "complete relief," and spent the next two days walking around the town sightseeing, without any of the after-effects she had previously experienced from walking.

3. A 62-year-old man. His knees had been stiff, painful, and inflamed for over two years, following an accidental fall onto his knees.

Arthroscopic examination revealed damaged cartilage in his right knee, and surgery was recommended to restore function. The patient refused surgery, even though he walked with difficulty and had to use his left leg (which was also affected) to lift himself slowly up steps. He said he had not slept well since he had developed the arthritis, because the pain woke him repeatedly during the night, and only the use of an analgesic would allow him to go back to sleep. He coated his knees and the skin around them, about four inches above and below, with a total of nearly an ounce of a solution similar to that used in case number two. Within 30 min, he appeared to able to walk more normally, and about 45 min after applying the solution, he remarked that he believed he was able to walk more easily.

He repeated the application that night before going to sleep. Around 10 o'clock the next morning, he returned and laughingly demonstrated his knees by running up the stairs, and said that he had been able to sleep through the night for the first time in years, and had not taken his usual analgesic. Topical treatment was discontinued after a few days, and he remained free of symptoms while taking 60 mg of pregnenolone orally, daily.

4. A 61-year-old woman. Painful and stiff joints in her hands had interfered with her work as a musician, and had made it impossible to sleep through the night, since the pain woke her two or three times during the night. A solution similar to that used in cases three and four was applied to the painful joints early in the evening, and a few hours later she was able to go to sleep without taking aspirin and slept through the night. She occasionally uses the same solution preventatively, and has not had a recurrence of the joint pain or stiffness.

We often hear that "there is no cure for arthritis, because the causes are not known." If the cause is an imbalance in the normal hormones of adaptation and resistance, then eliminating the cause by restoring this balance will produce a true cure.

Informed patients who suspect that their health problems are related to stress should encourage their physicians to investigate the use of thyroid hormone, progesterone, pregnenolone, DHEA, and the anti-stress nutrients, especially magnesium and vitamins A and E.

Immunity, Hormones and Yeast Infections

Townsend Letter for Doctors, October, 1985

In understanding candidiasis, two things, related to each other, are of special importance: the involvement of the endocrine system, and the suppression of natural immunity. Similar endocrine and immune problems can occur in other situations: cancer, aging, viral infections, and chemical poisoning. Damaged cellular respiration appears to be the common mechanism. A skin test, using Candida antigen, based on the universal exposure and acquired immune reactivity to it, shows a similar lack of response in both systemic candidiasis patients and in cancer patients. In a study of cancer patients, nutritional supplementation increased skin reactivity and survival. According to R. A. Cox, energy of the cell-mediated immunity and a T-cell deficiency are found in chronic mucocutaneous candidiasis. In 1860, Trousseau said that candidiasis is "the local expression of a very bad state of the whole system." Similar observations have been made regarding cancer and tuberculosis.

Thyroid, progesterone and pregnenolone help to normalize blood sugar by improving respiration, and should be the basic treatment for allergies.

Another surprising similarity between candidiasis and cancer is that the antibody reaction might be harmful, rather than helpful. According to Diamond, "high levels of specific antifungal antibodies may sometimes block or inhibit the development of cell-mediated immunity to mycoses."

Simplified ideas of the immune system were fostered by the success of vaccination against certain diseases, and by the preference of most researchers for clearly defined single-level mechanisms. Influences from the environment, nutrition, hormones, and biological rhythms make the problem more complex, but few people have recognized the importance of nonspecific immunity and the organism's general resistance. Early in this century, light therapy was recognized to be effective for tuberculosis. Coley's toxins were another early and successful attempt to stimulate the immune system. W. F. Koch, working in Gomberg's lab with free radicals, postulated that free radical oxidation was central to natural resistance to infection and cancer. Similar ideas were developed by Albert Szent-Györgyi, and many others contributed supporting evidence

for the importance of respiration in resistance to disease—Otto Warburg, Max Gerson, and Broda Barnes, for example.

The two hormones, estrogen and cortisone, are associated with stress, with respiratory changes and with changes in the immune system.

A recent review article by C. J. Grossman[1] outlines the effects of estrogen on the immune system. Estrogen causes atrophy of the thymus, and depresses the circulating levels of thymosin alpha one: when estrogen is given to castrated rats, their serum has "a marked inhibitory effect on T-cell function," and "estrogen and androgen act mainly to suppress the cell-mediated immune system." Estrogen increases antibody production, which is not necessarily helpful in conditions such as candidiasis and cancer. Estrogen retards skin graft rejection, and this probably indicates how parasites will be handled.

An especially important effect of estrogen is its reduction of the amount of IgA antibody secreted at membranes—this is very likely to be the reason for the high incidence of vaginal yeast infections premenstrually and during pregnancy. Thyroid and progesterone both increase the secretion of IgA, and these hormones are frequently deficient premenstrually and in pregnancy.

Allergy and epilepsy consist of hyperactivity of, respectively, immune cells and nerve cells. Low cellular energy, caused by hypoglycemia or hypoxia, causes hyperactivity of any cell type; the easiest way to observe this phenomenon is in the delayed relaxation of a hypothyroid person's Achilles reflex, or a delayed repolarization wave in the electrocardiogram. Estrogen interferes with cellular energy in many ways, including a contribution to hypoxia by impairing oxygen absorption. Thyroid, progesterone, and pregnenolone help to normalize blood sugar by improving respiration, and should be the basic treatment for allergies.

Some fungi have been found to respond to the human sex steroids, estrogen and testosterone, and there is evidence for a corticosteroid receptor in Candida[2] suggesting that the yeast produces and responds to a hormone resembling cortisone. Estradiol, the most powerful human estrogen, has been extracted from a yeast.[3]

For many years, male beer drinkers have been known to develop breasts. Since liver damage causes abnormal amounts of estrogen to be produced and retained, the alcohol was blamed, but in the last year, enough estrogen was found in beer and wine to account for the condition, independently of any alcohol damage to the liver. Bread was also found to

contain significant amounts of estrogen, from the yeast. (The increased rate of cancer which has been observed in beer drinkers might have something to do with estrogen. It would be interesting to compare the cancer incidence among bread eaters with the incidence in people who eat tortillas, pasta, or potatoes.)

Since early in this century, brewers' yeast was used for treating diabetes. The pancreas has an estrogen receptor, and estrogen promotes insulin secretion. Since reading of yeasts' responsiveness to sex hormones, about 15 years ago, I have encouraged people to use liver when they need a vitamin-mineral supplement, and to restrict the use of brewers' yeast mainly to the treatment of diabetes.

Besides people who are debilitated from starvation, drug treatment, or old age, the main groups who have a high incidence of Candida infection are diabetics, pregnant women, and premenstrual women. Rosalinde Hurley lists susceptible conditions, including infancy, severe infections, leukemia and other defects in cell-mediated immunity, and endocrine disease; she also mentions that the unhealthy skin near ulcers is often colonized by Candida.

A high glucose concentration in body fluids would be an obvious factor in diabetics, and in some pregnant women, but blood sugar tends to be low premenstrually. Many diabetics have high levels of cortisone, and some women do in pregnancy or premenstrually, but the consistent feature of pregnancy and the premenstrual part of the cycle is an increased production of the sex steroids.

Since progesterone used to be called the "luteal hormone," many doctors have wrongly associated it with many premenstrual events, including water retention. Most medical textbooks make the same mistake. The corpus luteum secretes both estrogen and progesterone, and when the person is under stress, progesterone production fails, while estrogen secretion continues. Progesterone deficiency and estrogen excess very often occur in the "luteal phase," premenstrually, and in pregnancy, and at menopause, with symptoms such as edema, emotional disturbances, blood clotting problems, and allergy symptoms. I think this misconception, that progesterone is "the luteal phase hormone," rather than the often deficient protective hormone, is what caused Dr. Truss to warn against its use in candidiasis patients. (Since most doctors prescribe synthetic progestins, with estrogenic and androgenic side effects, instead of natural progesterone, Truss's warning has probably helped some

women to escape that maltreatment.) Because of its effects on IgA, on blood sugar and the allergic reaction, and on the body's response to stress, natural progesterone would seem to be one of the most useful materials in treating candidiasis.

In the fungi which respond to the human sex steroids, these hormones function as sex hormones, or as sex pheromones—they attract the appropriate cell type, while causing changes in the cells which prepare them for conjugation.

In cell culture, virulent strains of Candida were found to adhere to cells from human membranes, while non-virulent strains didn't adhere. Also, the virulent forms of yeast adhered to cells taken from some people, and didn't stick to cells from other people. Even *in vitro* vaginal epithelial cells were more attractive to Candida—more yeasts adhered—when cells were from diabetics, pregnant women, or women near menstruation. This strongly suggests that glucose is not the regulating factor, since the glucose would be standardized in the culture fluid. More likely factors are estrogen, cortisone, the absence of an iron binding protein, or of bound antibodies; hypoxia causes increased cellular concentration of free fatty acids, so this is another possible factor.

The obvious next experiment will be to pretreat both yeast and donor cells with estrogens and other hormones including cortisone and testosterone, to see if virulence can be induced.

Estrogen and cortisone are things which suppress the host's immunity, and which appear to modify the fungus. Two other things, which have interesting connections with estrogen, can suppress immunity and stimulate yeast growth: unsaturated fatty acids and excess iron. Diamond has suggested that the reason candidiasis often occurs in leukemia is the high iron level in that disease; others have suggested that leukemia itself might be caused by an excess of iron, blocking the immune system. Iron (and high levels of zinc, i.e., 10 mM) stimulate the formation of mycelia (Hazen and Cutler, 1983).

In a low oxygen environment, unsaturated fatty acids can stimulate yeast growth,[4] and they suppress immunity in various ways.

Besides a direct effect on cellular immunity, unsaturated fatty acids interfere with thyroid function and with mitochondrial respiration. Low thyroid leads to high estrogen. Estrogen (and low thyroid) cause increased absorption of iron. At an extreme point, excess iron disturbs several endocrine glands, but at a more moderate level, it blocks cellular

immunity. Combined with unsaturated fatty acids, iron stimulates peroxidation, with toxic effects, including the formation of carbon monoxide, inhibiting respiration. Vitamin C stimulates the absorption of iron, and can also increase the rate of peroxide formation. In a special disease of iron retention, idiopathic hemochromatosis, vitamin C was found not to increase iron excretion when tested by itself, though it did increase the effect of a drug called deferrioxamine.[5]

The mitochondria are not only the site of respiratory energy production, but are where cholesterol is converted to pregnenolone, which is then converted to progesterone and DHEA. These steroids all appear to protect the respiratory system. This respiratory protection is probably part of what Selye called the "catatoxic" function, the fact that certain steroids, especially pregnenolone, protect organisms against a great variety of poisons.

Whether it is an exogenous chemical, or a poison produced by intestinal organisms, or a toxic effect of damage to one's own tissue, which is making a person sick, it would seem reasonable to use a protective, "catatoxic" material such as pregnenolone as part of the supportive therapy. Fiber, oxygen drinks, and aspirin can protect the bowel.

My first experiments with yeast were with the Koch reagents, but then I got interested in testing possible anti-iron substances. Caffeine, I suspect, uses that mechanism, among others. I have also experimented with essential oils, clove oil, thymol, and menthol, and elemental sulfur, which is probably the least toxic therapy for many fungus infections of the skin, vagina, and bowel. Lime-sulfur and other sulfur mixtures have a long history as fungicides. Saturated fatty acids generally inhibit fungal growth. Short chain acids, such as acetic, lactic, propionic, and caprylic acids have often been used as anti-fungals, and even the longer chain saturated fatty acids have been tested.

Large doses of vitamin A and potassium iodide have been used, separately and together, to promote general immunity, and also to treat fungus infections; I suspect that an effect of the iodide is to protect against the toxicity of the unsaturated fatty acids.

Thiosulphate is another form of sulfur that has been used for skin fungal infections. Many herbal drugs contain quinones and saponins which are active against fungi, but which can be dangerous to the patient. The imidazoles can be dangerous because they block steroid synthesis in the patient as well as in the fungus. Nystatin is also believed to act

on fungal steroids, and it can be toxic to the patient, but it is considered the best treatment for a deadly systemic infection (e.g., lungs, heart, kidneys). Desensitization with Candida vaccine and treatment with immune rabbit serum are discussed in R. Dubos's book, *Bacterial and Mycotic Infections of Man*. Boric acid (5 %), antihistamines, and many other chemicals have some anti-fungal activity, but except for sulfur, I think the best approach is to optimize the patient's resistance.

Inhibition and Vitality

Townsend Letter for Doctors, February, 1986

In the Achilles reflex test, slow relaxation of the calf muscle is used to demonstrate the low metabolism of hypothyroidism. In the high energy person, relaxation is instantaneous. This is a general principle for the brain and other tissues: the high energy state is relaxed.

Epilepsy is an example of a very low energy state of brain cells. Insomnia is a low energy state, and is usually cured by the right dose of thyroid hormone, with adequate glucose and other nutrients. Insomnia is extremely common in aging people, and is the main problem at menopause. Inflammation is another example of a low energy state. Specific patterns of symptoms can be produced by reflexes, and these reflexes can be stuck in place by an energy deficiency. Focused activity and an alert readiness to respond are prevented by a low energy state, which can cause us to get stuck in inappropriate activity, ranging from worry to "auto-immune" conditions.

The inhibited state of nerves has not been a popular field for research in our culture, but the knowledge gradually accumulates. Another type of inhibition has been described recently by Egan and North.[1]

Burton

Last year the Center for Disease Control tested some of Dr. Burton's immuno-augmentative therapeutic material, and found that 50 % of it was contaminated with AIDS virus (at least the antibodies), and that all of it tested positive for hepatitis. Since he had been getting all of his blood from the U.S., from commercial sources, this sounded suspicious.

In the 1960s he was highly respected. The year he got in trouble, 1975, was the year the cancer establishment decided to follow his leads in immunotherapy. Dr. Coley's toxins were removed from the "quack remedy" list. Last year, when Burton's institution was closed down because of the incredibly high rate of AIDS contamination, was the year that the biggest institutional researchers began their promotion of the tumor necrosis factor—which Burton discovered.

Burton used a variety of blood-derived materials, but purification will be necessary before a drug company can control it satisfactorily.

If the stuff doesn't kill people, along with the cancer, it also has great financial potential as a weight-loss drug. I have been trying to learn his side of the contamination story, so I recently tried calling his 800 number, but I was too late, and the woman who answered said she had no knowledge of his organization; she just worked for the U.S. Army. If you know his address, please let me know.

Black Body Radiation

A red hot object radiates lower energy, longer waves than a very hot star does, and a warm person radiates slightly longer, lower energy waves than does the red hot object. The peak of our radiant emission is long infrared, and we are fairly transparent to that wavelength, so we are black body emitters, regardless of our skin color. It has been calculated that 70 % of our metabolic energy is spent as radiation.

If we are surrounded by large amounts of mass at our own temperature, we will absorb about as much as we lose. Several years ago, lab rats were kept at a constant temperature, with constant 12 hour light periods, and were found to experience a decline in thyroid function during the winter. I had noticed a similar effect in hamsters, atrophy of the thymus gland in the late autumn. Since long-wave infrared and longer wavelength microwaves can penetrate walls to some extent, it could be that the absence of that kind of radiation during the winter is the stressor which causes these changes, and the mitochondrial damage which occurs in the winter.

It could be that some of the therapeutic effects of natural hot springs are caused by gently appropriate radiation from the large masses of hot earth in the vicinity. I think these longer waves might also have an anti-free radical effect, possibly by acting on solvated electrons.

Forests

In the early 1950s I went back to a stream I had seen a couple of years earlier, in southern Oregon; it was one of the most beautiful places I had seen. On my second visit, it had been absolutely destroyed by loggers, who had bulldozed earth, broken logs, and rocks into it. It was just one of the many small streams where fish used to spawn, that have now been destroyed by loggers. A forester has said that much of southern Oregon

will never be able to grow forests again, because the soil was eroded after the trees were cut.

A recent news item mentioned that the Atacama desert in Chile also used to be a humid coastal forest, and that it was destroyed by loggers. Another news item mentioned that removal of trees from the Mexican hill where the Monarch butterflies migrate for the winter was lowering the humidity to such an extent that the butterflies might not be able to survive, even though their own trees are not removed. This effect of trees on humidity is very important, but it is usually overlooked. The concept of "desertification" is widely accepted when it is applied to another continent (the Sudan, for example), but not when it might relate to a local resource which supports the area's biggest industry.

When I first went to Mexico in 1955, I was shocked by the huge gullies that were being eroded through the dark brown soil of the hilly grass-covered expanses in the western part of the State of Mexico. In later years those sharp cuts through the muddy earth had disappeared, and a smooth contour had returned, but the remaining soil was pale and rocky, and barely supported grass. A few years ago I learned that this region had been covered by the same dense pine forests which still exist in some parts of the State, but that a foreign company had removed the forests early in this century. A place there is still called El Yukon.

Now that most of the forests, from the California redwoods into Washington, have been destroyed, the center of the logging industry has moved north into Canada. Foresters describe the logging technique used there as "extraction," and say it won't be long until their forests are depleted, so that maybe Oregon's forests will regain their competitive position. Canada's Yukon might someday resemble El Yukon in Mexico.

When a region doesn't go directly from a conifer forest to a desert, it may be replaced by deciduous shrubs and trees. The ultimate outcome of this replacement is unknown, but I think we are already seeing some of the effects. Conifers are good at conserving water: they transpire sparingly in the hot, normally dry summers of the Pacific coast region, but they do transpire a little in the winter. Humid air is lighter than dry air: a massive forest allows ocean air to circulate over the land in winter, yet a conifer forest does not extravagantly increase the humidity in the summer. A deciduous forest, leafless in winter, allows dense cold dry air to accumulate, which diverts the humid ocean air. In the summer, however, their intense transpiration tends to intensify the entry of air

from the ocean, with the result that rainfall tends to become seasonally reversed, and some of the winter moisture is dumped further south.

People who defend the lumber industry's practices say that the forces controlling weather are too big to be influenced by human activity, but several studies show otherwise. For example, the absence of vegetation in the city of St. Louis causes such intense summer heating and updrafts that corn production has doubled in an area down-wind, from the resulting increase in the summer rainfall.

Caffeine

A study in Israel, where there has been no publicity about a connection between caffeine and breast disease, found that using caffeine or avoiding it had no effect on breast disease. A letter in *JAMA*[2] says "most reports show no significant correlation between fibrocystic disease and methylxanthine intake." He says "there was considerable evidence to suggest that caffeine has antineoplastic effects." He also says that "caffeine intake had a significant association with tumor differentiation…Since poor tumor differentiation is linked with decreased survival, the question is raised whether caffeine may have had a beneficial effect in these women." All of the experiments in cell culture similarly suggest that caffeine might be beneficial.

Cystic Fibrosis

Several years ago a "mutation" was discovered in a regional primate center which was said to be equivalent to human cystic fibrosis. A researcher there couldn't believe that an identical mutation could have appeared at the same time in five or six apes: he believed that their symptoms resulted from poisoning from the large amounts of unsaturated vegetable oil they were being fed. He was fired immediately: the new "gene" would have brought in large amounts of research money. A recent study of young adults with cystic fibrosis found that they had low serum levels of both selenium and vitamin E. This seems to support the ex-scientist's theory.[3]

Food Radiation

As sulfite is removed from foods, pressure will increase for wider use of radiation to extend shelf life of many foods. Proponents are saying that some public education will be necessary, because radiation causes instantaneous changes which modify flavor and texture of foods, making people think they are not fresh: people must be informed, they say, to realize that the spoiled taste and consistency actually means greater freshness, since their shelf life has been extended by many weeks.

Radiation, of course, stimulates oxidation of fats, among other changes (called "unique radiolytic products," URP), and rancid fat is toxic and carcinogenic.

Insomnia & Hyperactivity

Townsend Letter for Doctors, April, 1994

SOMETIME after my teens, I became a light sleeper. I found that if I stayed up too late it was hard for me to go to sleep, and then when I slept it was restless and dream-disturbed sleep. I suspected that my hormonal state was in some way analogous to that of new mothers, who wake at the slightest sound from their infant. A friend of mine had an episode of psychosis after her child was born, and I began to think about the frequent association of post-partum hypothyroidism with emotional or perceptual problems. Although I tended to be hypermetabolic, and had been puzzled for years about the co-existence of signs of both hyper- and hypothyroidism, I finally tried taking thyroid. Immediately, I was able to sleep easily and deeply, and my need for food decreased. It was obvious that thyroid was having a quieting effect on my whole metabolism. I slept more efficiently, woke up refreshed, and had abundant energy during the daylight hours, and began looking for chores to do around the house, just for fun. Before taking thyroid, the first thing I did every morning was to drink two or three cups of coffee, but a few days after taking thyroid I noticed I didn't think about coffee very often, and I drank about 90 % less, without feeling any withdrawal symptoms.

Since the 1960s, a stimulant, Ritalin (methylphenidate) has often been prescribed for hyperactive kids, because it made them able to quietly pay attention. This effect was called "paradoxical," but—for scientific physiology—there was nothing paradoxical about it. The frontal lobes of the brain, the most highly evolved part, give us the ability to plan and to understand complex things that require prolonged attention. Without this higher part of the brain which has a very high energy requirement, people and animals become hyperactive and unable to concentrate. Ritalin (or coffee) makes anyone, even the brightest students, more attentive and focussed. Caffeine and Ritalin temporarily raise the energy level of the brain. Thyroid hormones are essential for providing the energy to keep the brain at a high energy level all the time. If these hormones are deficient, our nerves need stimulants to function normally, and our bodies ordinarily produce large amounts of adrenalin to keep us going. The result is that we get tired and tense at the same time.

An old and useful test of thyroid function uses the Achilles tendon reflex, to observe the relaxation speed of the calf muscle. In hypothyroid states, the muscle is slow to relax, because the cells are slow to replace the energy used by the contraction-twitch. Because of the slow energy production, the muscles tend to fatigue easily, and to swell and feel sore with moderate exercise. In children, painful, swollen and tense muscles sometimes make it hard to go to sleep after an active day.

In the heart, slow replacement of energy can be seen in the EKG, as a delayed and depressed T wave; if this is combined with stress and excitement, it can cause a rhythm disturbance.

The brain is just like muscle, in having to restore its energy to relax. Many people have noticed that eating a lot of carbohydrate and/or salt makes them sleepy. Both salt and carbohydrate tend to lower adrenalin, and carbohydrate can also increase the activity of thyroid hormone, while restoring energy to the tissues.

In the last 20 years, I have seen almost everyone's insomnia disappear when they correct their hypothyroidism, sometimes just with dietary changes, but more often with a thyroid supplement. Many times, people have told me that they get to sleep within a few minutes when they take a minimal dose of thyroid at bedtime. By increasing the rate of energy production, relaxation and sleep are made possible.

In 1973 (in my book, *Mind and Tissue*) I reviewed old studies of cellular inhibition, which distinguished between the naturally quiet resting state of energized cells, and the state of protective inhibition, which prevents injury or death from overstimulation and fatigue. In our "establishment physiology," there has been no coherent theory of cellular inhibition, which means that cellular activity could hardly be understood correctly, either. Most of the facts are known, but they have seldom been put together in meaningful patterns, which would let us see that a few simple principles govern a great range of disturbing phenomena: seizures, shock, hypertension, fibrillation, cramps, restless legs, coma, insomnia, obsessive thinking, migraine, hyperactivity, even cell death and aging.

Coherent theories have been rejected because they don't suit the dogma of the establishment physiologists, who like to explain things in terms of hypothetical "membrane pumps." A few fetish ideas dominate physiology, just as the gene and virus fetishes have governed cancer research. For more than a century, most physiologists have "explained"

muscle soreness as being "caused by lactic acid," while generally ignoring the great swelling of muscles that results from intense exercise. When cells don't have enough energy—whether from inadequate fuel, overwork, lack of oxygen, or poisoning—they take up water. Too much water tends to excite the cells, and can even stimulate cell division. The hyperactive state of a muscle cell, cramping, causes energy to be spent. What is too often overlooked is that the cell needs more energy to get back into its resting state, and that an abundance of glucose or other fuel, oxygen, and thyroid are needed for the cell to produce energy fast enough to become quietly relaxed.

Albert Szent-Györgyi demonstrated that rigor mortis, the stiffening of the body that occurs after death, is just an energy deficiency, like a final cramp: he injected ATP (the tissue "energy molecule") into a stiff animal, and its tissues' softness was restored. The idea of "membrane pumps" keeps many people from seeing the implications of experiments like that. Intravenous injection of ATP cures shock, restoring normal circulation and tissue function, but again, the idea of membranes and their pumps has kept mainline science on its relatively sterile track.

The reluctance to see something as simple as the swelling of a muscle when its energy is depleted, has led into other unnecessary confusions. For example, the water that the muscle takes up comes from the blood. The blood gets thicker, and is harder to pump. The loss of water from the blood makes it seem that hormones have increased, when actually they may have decreased. If the tissues could be re-energized, they would release some of their water back to the blood.

For many years, a few physicians have known about the quieting effects of thyroid, and have prescribed it for hyperactive kids, as well as for lethargic ones, and for otherwise healthy kids with "growing pains." Since the mid-1950s, there has been a terrible increase in the incidence of hyperactivity in children, as discussed by Tom Brewer, largely because of prenatal injury. The increased use of unsaturated vegetable oils (proven to cause brain damage in rats) has certainly played a role. The more unsaturated an oil is, the more strongly it interferes with thyroid secretion, the transport of thyroid hormone in the blood, and the response of the tissue thyroid receptors. Hypothyroidism, both prenatally and during childhood, severely limits development of the brain.

It is a simple fact that nerve cells must have an abundance of energy if they are to be able to relax. Every physician knows about the convulsions produced by extreme hypoglycemia, and some know that a lack of oxygen can produce convulsion, but few realize that a high energy state is needed for stable nervous relaxation. Otherwise, no one would hesitate to use thyroid hormone (and its energy-associated co-factor, magnesium) for insomnia, hyperactivity, and the whole range of energy-related problems.

(Incidentally, thyroxine alone can be counter-productive, by competing with the respiration-promoting triiodothyronine, and by suppressing TSH secretion even when T_3 is deficient. Similarly, a normal or high level of thyroxine in the blood doesn't mean that the person isn't hypothyroid, since T_3 is the active hormone. Most of our T_3 is produced in the liver.)

Iodine Injections

Townsend Letter for Doctors, October, 1986

YOU mentioned in the July *Letter* that iodine injectors have been used in atherosclerosis. An old PDR described the use of iodide in atherosclerosis. Could you tell me who has studied the iodine injections? I liked your comments on chelation.

Iron: Cumulative Danger

Townsend Letter for Doctors, June, 1997

Q: You believe iron is a deadly substance. Why?

Iron is a potentially toxic heavy metal. In excess, it can cause cancer, heart disease, and other illnesses.

Q: Could you tell us about some of these studies?

In the 1960s the World Health Organization found that when iron supplements were given to anemic people in Africa, there was a great increase in the death rate from infectious diseases, especially malaria.

Around the same time, research began to show that the regulation of iron is a central function of the immune system, and that this seems to have evolved because iron is a basic requirement for the survival and growth of cells of all types, including bacteria, parasites, and cancer. The pioneer researcher in the role of iron in immunity believed that an excess of dietary iron contributed to the development of leukemia and lymphatic cancers.

For about 50 years, it has been known that blood transfusions damage immunity, and excess iron has been suspected to be one of the causes for this. People who regularly donate blood, on the other hand, have often been found to be healthier than non-donors, and healthier than they were before they began donating.

Just like lead, mercury, cadmium, nickel, manganese and other heavy metals, stored iron produces destructive free radicals. The harmful effects of iron-produced free radicals are practically indistinguishable from those caused by exposure to X-rays and gamma rays; both accelerate the accumulation of age-pigment and other signs of aging. Excess iron is a crucial element in the transformation of stress into tissue damage by free radicals.

In one of Hans Selye's pioneering studies, he found that he could experimentally produce a form of scleroderma (hardening of the skin) in animals by administering large doses of iron, followed by a minor stress. He could prevent the development of the condition by giving

the animals large doses of vitamin E, suggesting that the condition was produced by iron's oxidative actions.

Many recent studies show that iron is involved in degenerative brain diseases, such as Parkinson's, ALS (Lou Gehrig's disease), Huntington's chorea, and Alzheimer's disease. Iron is now believed to have a role in skin aging, atherosclerosis, and cataracts of the lenses of the eyes, largely through its formation of the "age pigment."

Q: How does excess iron accelerate our aging process?

During aging, our tissues tend to store an excess of iron. There is remarkably close association between the amount of iron stored in our tissues and the risk of death from cancer, heart disease, or from all causes. This relationship between iron and death rate exists even during childhood, but the curve is downward until the age of 12, and then it rises steadily until death. The shape of this curve, representing the iron burden, is amazingly similar to the curves representing the rate of death in general, and the rate of death from cancer. There is no other relationship in biology that I know of that has this peculiar shape, with its minimum at the age of 12, and its maximum in old age at the time of death.

One of the major lines of aging research, going back to the early part of this century, was based on the accumulation of brown material in the tissues known as "age-pigment." The technical name for this material, "lipofuscin," means "fatty brown stuff." In the 1960s, the "free radical theory" of aging was introduced by Denham Harman, and this theory has converged with the age-pigment theory, since we now know that the age-pigment is an oxidized mass of unsaturated fat and iron, formed by uncontrolled free radicals. Until a few years ago, these ideas were accepted by only a few researchers, but now practically every doctor in the country accepts that free radicals are important in the aging process.

A nutrition researcher in San Diego suspected that the life-extending effects of calorie restriction might be the result of a decreased intake of toxins. He removed the toxic heavy metals from foods, and found that the animals which ate a normal amount of food lived as long as

the semi-starved animals. Recently, the iron content of food has been identified as the major life-shortening factor, rather than the calories.[1]

Q: Exactly how much iron do we need to eat?

Children's nutritional requirements are high, because they are growing but there are indications that in the U.S. even children eat too much iron. Some researchers are concerned that the iron added to cereals is contributing to the incidence of leukemia and cancer of the lymphatic tissues in children.[2] During the time of rapid growth, children are less likely than adults to store too much iron. At birth, they have a large amount of stored iron, and this decreases as they "grow into it." It is after puberty, when growth slows and the sex hormones are high, that the storage of iron increases.[3]

In a study of the "malnourished" children of migrant fruit pickers in California, these children who were "seriously anemic" were actually more resistant to infectious diseases than were the "well-nourished" middle class children in the same region.

If the normal amount of dietary iron causes an increased susceptibility to infections even in children, and if a subnormal amount of iron slows the aging process, I think we are going to have to reconsider our ideas of nutritional adequacy, to look at the long range effects of diet, as well as the immediate effects. My current studies have to do with analyzing our ability to handle stress safely, in relation to our diet. I believe our nutritional recommendations for iron have to be revised sharply downward.

Q: Don't women need extra iron?

That's a misunderstanding.

Doctors generally don't realize that only a few milligrams of iron are lost each day in menstruation. The real issue is that you can hardly avoid getting iron, even when you try.

Women absorb iron much more efficiently than men do. From a similar meal, women will normally absorb three times as much iron as men do. When pregnant, their higher estrogen levels cause them to absorb about nine times as much as men. Every time a woman menstruates, she loses a little iron, so that by the age of 50 she is likely

to have less iron stored in her tissues than a man does at the same age, but by the age of 65 women generally have as much excess iron in their tissues as men do. (During those 15 years, women seem to store iron at a faster rate than men do, probably because they have more estrogen.) At this age their risk of dying from a heart attack is the same as that of men.

Some women who menstruate can donate blood regularly without showing any tendency to become anemic,

Since the custom of giving large iron supplements to pregnant women has been established, there has been an increase in jaundice of the newborn. It has been observed that women who didn't take iron supplements during pregnancy have healthy babies that don't develop jaundice. I have suggested that this could be because they haven't been poisoned by iron. Those supplements could also be a factor in the increased incidence of childhood cancer.

Q: Don't you need iron supplements if you are anemic?

In general, no.

Many doctors think of anemia as necessarily indicating an iron deficiency, but that isn't correct. One-hundred years ago, it was customary to prescribe arsenic for anemia, and it worked to stimulate the formation of more red blood cells. The fact that arsenic, or iron, or other toxic material stimulates the formation of red blood cells doesn't indicate a "deficiency" of the toxin, but simply indicates that the body responds to a variety of harmful factors by speeding its production of blood cells.

Even radiation can have this kind of stimulating effect, because growth is a natural reaction to injury. Between 1920 and 1950, it was common to think of "nutritional growth factors" as being the same as vitamins, but since then it has become common to use known toxins to stimulate the growth of farm animals, and as a result, it has been more difficult to define the essential nutrients. The optimal nutritional intake is now more often considered in terms of resistance to disease, longevity or rate of aging, and even mental ability.

An excess of iron, by destroying vitamin E and oxidizing the unsaturated fats in red blood cells, can contribute to hemolytic anemia, in which red cells are so fragile that they break down too fast.

In aging, red cells break down faster, increasing the tendency to become anemic, but additional iron tends to be more dangerous for older people.

Anemia in women is caused most often by a thyroid deficiency, or by various nutritional deficiencies.

Estrogen (even in animals that don't menstruate) causes dilution of the blood, so that it is normal for females to have lower hemoglobin than males.

Q: What should I do if my doctor tells me I'm anemic? Is there any situation in which a person needs to take iron supplements?

Iron deficiency anemia does exist, in laboratory situations and in some cases of chronic bleeding, but I believe it should be the last-suspected cause of anemia, instead of the first. It should be considered as a possible cause of anemia only when very specific blood tests show an abnormally low degree of iron saturation of certain proteins.

Usually, physicians consider the amount of hemoglobin or of red cells in the blood as the primary indicator of a need for iron, but that just isn't biologically reasonable.

If a large amount of blood is lost in surgery, a temporary anemia might be produced, but even then it would be best to know whether the iron stores are really depleted before deciding whether an iron supplement would be reasonable. Liver (or even a water extract of wheat germ) can supply as much iron as would be given as a pill, and is safer.

Q: What foods contain iron?

Flour, pasta, etc., almost always contain iron which has been artificially added as ferrous sulfate, because of a federal law. Meats, grains, eggs, and vegetables naturally contain large amounts of iron. A few years ago, someone demonstrated that they could pick up a certain breakfast cereal with a magnet, because of the added iron.

Black olives contain iron, which is used as a coloring material. You should look for "ferrous" or "ferric" or "iron" on the label, and avoid foods with any added iron. Many labels list "reduced iron," meaning

that iron is added in the ferrous form, which is very reactive and easily absorbed.

Q: Why does federal law require the addition of iron to those foods?

Industrially processed grains have most of the nutrients, such as vitamin E, the B vitamins, manganese, magnesium, etc., removed to improve the products' shelf life and efficiency of processing, and the government required that certain nutrients be added to them as a measure to protect the public's health. But the supplementation did not reflect the best science even when it was first made law, since food industry lobbyists managed to impose compromises that led to the use of the cheapest chemicals, rather than those that offered the greatest health benefits.

For example, studies of processed animal food had demonstrated that the addition of iron (as the highly reactive form, ferrous sulfate, which happens to be cheap and easy to handle) created disease in animals, by destroying vitamins in the food. You should read the label of ingredients and avoid products that contain added iron, when possible.

Q: Can cooking in an iron frying pan put iron into food?

Yes, especially if the food is acidic, as many sauces are. The added iron will destroy vitamins in the food, besides being potentially toxic in itself.

Q: What about aluminum?

Aluminum and iron react similarly in cells and are suspected causes of Alzheimer's disease.

The aluminum industry started propagandizing more than 50 years ago about the "safety" of aluminum utensils, claiming that practically none of the toxic metal gets into the food. Recent research showed

that coffee percolated in an aluminum pot contained a large amount of dissolved aluminum, because of coffee's acidity.

Q: What kinds of cooking pots or utensils are safe?

Glass utensils are safe, and certain kinds of stainless steel are safe, because their iron is relatively insoluble. Teflon-coated pans are safe unless they are chipped.

Q: How do I know which stainless steels are safe?

There are two main types of stainless steel, magnetic and nonmagnetic. The nonmagnetic form has a very high nickel content, and nickel is allergenic and carcinogenic. It is much more toxic than iron or aluminum. You can use a little "refrigerator magnet" to test your pans. The magnet will stick firmly to the safer type of pan.

Q: Why is there iron in most multi-vitamin and mineral products?

Although several researchers have demonstrated that iron destroys vitamins, there is enough wishful thinking in industry, government, and the consuming public, that such mistakes can go on for generations before anyone can mobilize the resources to bring the truth to the public.

Ten years ago, I thought it was a hopeful sign of increased awareness of iron's danger when the manufacturer of a new iron product mentioned in the Physician's Desk Reference that it hadn't yet been reported to cause cancer.

Q: I can't avoid all those foods, especially the bread and grains. What can I do to keep the iron I ingest from harming me?

Iron destroys vitamin E, so vitamin E should be taken as a supplement. It shouldn't be taken at the same time as the iron-contaminated food, because iron reacts with it in the stomach. About 100 mg per day is adequate, though our requirement increases with age, as our tissue iron stores increase.

Coffee, when taken with food, strongly inhibits the absorption of iron, so I always try to drink coffee with meat.

Decreasing your consumption of unsaturated fats makes the iron less harmful.

Vitamin C stimulates the absorption of iron, so it might be good idea to avoid drinking orange juice at the same meal with iron-rich foods.

A deficiency of copper causes our tissues to retain an excess of iron, so foods such as shrimp and oysters which contain abundant copper should be used regularly.

Q: How does copper help us?

Copper is the crucial element for producing the color in hair and skin, for maintaining the elasticity of skin and blood vessels, for protecting against certain types of free radical, and especially for allowing us to use oxygen properly for the production of biological energy. It is also necessary for the normal functioning of certain nerve cells (substantia nigra) whose degeneration is involved in Parkinson's disease. The shape and texture of hair as well as its color, can change in a copper deficiency.

Too much iron can block our absorption of copper, and too little copper makes us store too much iron. With aging, our tissues lose copper as they store excess iron. Because of those changes, we need more vitamin E as we age.

Summary

1. Iron is a potentially toxic heavy metal; an excess can cause cancer, heart disease, and other illnesses.
2. Other heavy metals, including lead and aluminum are toxic; pans and dishes should be chosen carefully.
3. Iron causes cell aging.
4. Drinking coffee with iron-rich foods can reduce iron's toxic effects.
5. Use shrimp and oysters, etc., to prevent the copper deficiency which leads to excess storage of iron.
6. Avoid food supplements which contain iron.
7. Take about 100 units of vitamin E daily; your vitamin E requirement increases with your iron consumption.

Notes

A Finnish study, two years ago indicated that high iron stores may increase heart attack risk.[4] Dr. Jerome L. Sullivan, director of clinical labs of Veterans Affairs Medical Center at Charleston, South Carolina, in 1983 proposed that excess iron contributes to heart attacks. University of Kuopio in Finland: Large-scale study (nearly 2,000 men, for up to five years); next to smoking, excess stored iron is the most significant identifiable risk factor for heart attacks. It is a stronger risk factor for heart attack than high blood pressure and cholesterol.

U.S. studies showed a weak connection between iron and heart disease,[5] and a weak connection with the iron in red meat. Epidemiologists at the Pacific Northwest Laboratory in Washington have reported that the greater the concentration of iron in a person's blood, the greater his or her risk of cancer. Richard Stevens and his co-workers found the connection from examining cancer rates in more than 8,000 people who participated in the 1971 National Health and Nutrition Examination survey. A second Finnish study with similar findings accompanied Steven's report in the *International Journal of Cancer*, and suggests that there may be cause for concern.

Associated Press: 1982-92, heart disease death rate dropped 24.5 %; number of cases of congestive heart failure doubled during roughly the same period. It killed 39,000 Americans in 1991, costs system $40 billion per year. Cancer is the biggest killer of women under 64, heart disease far surpasses cancer in women of ages 65–84.[6]

Moles, DHEA, etc.

Ray Peat's Newsletter, 2015

EVERYONE knows what a mole is, but no one understands what a mole really is. Moles are interesting because they are simultaneously normal and a little abnormal. But it seems that no one has taken them seriously enough to study them very scientifically. At least, I don't know of any publications on "the epidemiology of moles," or "the experimental production of moles."

Advertisements from the cancer society fundraisers have taught people that "any change" in a mole could be a sign of cancer. The idea seems reasonable enough, but I think it has no clear scientific basis The fear of cancer has caused many people to have things excised as soon as they are noticed, but during this generation in which people have learned to have things cut out promptly, the incidence of melanoma has risen sharply. Melanoma first appears in normal-looking skin about as often as it does in pigmented moles, so the "preventive" removal of all moles is no guarantee that you won't get melanoma.

At least some pigment cells are "amoeboid," meaning that they can creep around. At body temperature, white blood cells under the microscope can walk about two inches per day.[1] These facts indicate that it could be seriously misleading to think of a bit of tissue, such as a mole, as a "strictly localized" thing, the removal of which has no meaning for the rest of the body.

I will just briefly mention some of the observations that have made me think of moles as "systemic phenomena."

A friend had many protuberant moles that had been present for most of her life (if not since birth), and one summer they withered, dried up, and fell off. She was taking a little more thyroid and triiodothyronine that summer.

One hot summer, I had a four ounce glass of Modelo beer, discovered I liked it, and for the rest of the summer I would often drink a similar small amount during he hot part of the day, while at my friend's house to water the plants. Two moles appeared on my forehead, and grew rapidly, until the bigger one was the size of a small pea. When the beer in the refrigerator was gone, the summer was nearly over, and I had thought increasingly about the estrogen content of beer, so I didn't drink any

more. Within about a week, the moles were shrinking. The smaller one disappeared while the other one was still about the size of match-head. After about three weeks, the remaining mole was about the size of a dried pea, and one morning it rolled free when I touched it. It had become firm and dry.

DHEA Changes Moles

In 1980, a familiar old mole on my belly had begun growing and darkening. A couple of times when I had my shirt off on a hot day physician friends looked worried when they saw it and told me I'd better have it removed. It became thoroughly black, took on a sharply triangular shape, and had a firm leathery texture. By 1981, it was about 15 mm long, but still fairly flat. I had been experimenting with oral doses of DHEA in oil for two or three weeks, and had noticed that it made me feel like an adolescent, but it was causing me to get pimples.

One night as I was going to bed, I looked down and was shocked to see what looked like a maraschino cherry on my belly. I spontaneously flicked at it with my finger, thinking it might be an engorged tick, though the color and gloss weren't appropriate. Just before the second flick brushed it, I too late saw something black on the top of the globe, and realized that it was my mole. The black material brushed away, leaving a small drop of blood, but the dome remained glossy and red. By the next day, it was smaller and was no longer shiny from internal pressure. That afternoon I photographed it, and there was a red flare surrounding it, about 2 inches in diameter. By the third day, I could see that the deflating thing was going to be a brown mole, of roughly the same size as the original one that had been there a few years earlier. The only difference from its earlier state is that its margin might be more diffuse now.

In his mid-50s, my brother mentioned that he was getting a mole-like spot on his forehead. When I told him about my experience, and that I thought oral DHEA might have been responsible for the mole's disappearance, he applied a concentrated solution of DHEA in vitamin E directly onto the mole. A day or two later, he noticed a spot of blood on his pillow, and had his doctor cut the thing off, because of fear that bleeding signalled a malignant change.

After I found that a copper solution quickly caused my white eyebrows to return to their normal color, and repeated the experiment sev-

eral times over about 3 years, I tried the same solution on my sideburns, and saw that some of those hairs had darkened after one application. It wasn't convenient to observe those hairs, so I decided to apply the solution to some white whiskers on my chin. After two or three applications, I carelessly used a solution that was too strong. Within less than a minute I felt it stinging, and washed it off. A stinging sensation was noticeable during the next 2 or 3 h, and I washed the spot thoroughly several times. About 4 h later it was still a little uncomfortable, and when I looked at it in a mirror I was horrified to see what appeared to be a large, coffee-colored mole on my chin, in the area where I had applied the copper, and where the burning sensation persisted. The edges were slightly raised about the surrounding skin, and it looked li ke a normal light brown mole, roughly the size of a nickel.

It was so hard for me to believe that such an anatomical change could have occurred within 4 h that I wondered if I had just failed to observe something that had been developing gradually.

But after about a week it had disappeared, and no trace of it has returned, so I had to conclude that the high concentration of copper had acted with, or in place of, tyrosinase to form new pigment, or that copper-hungry cells had invaded the area.

A couple of years ago I noticed some moles on my upper chest were growing, darkening and developing an irregular, granular form. I hadn't used any DHEA for a few years, just because I had lost interest in it. A friend had just been telling me about using topical progesterone and DHEA in vitamins E and A to shrink a large and growing mole on her leg. For a few weeks I watched carefully as my moles changed since their location made it easy for me to view them at very close range. After becoming nearly black, I noticed that they were fading and becoming sort of grey. Then white and creamy areas appeared, and the grey seemed to concentrate into a few blue spots. The changes were surprisingly fast. I would look at them 2 or 3 times a day, and the blue, or black, or brown spots would be in entirely different locations each time. The moles had become firm to touch, but the spots of pigmented cells appeared to be swimming wildly around within the boundaries of the moles, as if looking f or something, or escaping from something. I smeared a very light film of vitamins A and E with DHEA over the area of my chest with the moles, and the next time I looked the color was becoming regular. Within a day or two, even the texture had returned to normal.

Higher Altitudes Decreases Cancer Incidence

About ten years ago, a cancer geographer mentioned that he had found an inverse relation between altitude and the incidence of cancer around the world. A woman from Texas who was at the conference was sure his information was wrong, because the higher intensity of "radiation" at high altitudes would increase the damage to DNA that is commonly supposed to cause cancer. She decided to disprove his work by doing a study limited to the incidence of melanoma—which is supposed to be especially sensitive to ultraviolet radiation—within Texas. Her results surprised her; even melanoma incidence was lower at higher elevations.

Much of the doctrine about radiation at high altitude has been created by and for the nuclear industry. Actually, the dangerous secondary and tertiary particle showers from cosmic rays are more intense at sea-level than at high altitudes. But the greater oxygen pressure at sea-level might be the most important factor in various kinds of cancer, and other disease, since our antioxidant system can probably maintain better balance at high altitude. Mitochondria become more numerous at high altitude, and this might result from increased durability, as well as from the need for more efficient use of oxygen.

The skin is a major source of sterol formation. Skin changes in aging might indicate a special susceptibility to sterol deficiency, which could make topical application of steroid-associated materials especially appropriate.

About 50 years ago, melanosomes were believed to develop from mitochondria. Whether that was accurate or not, there are some interesting parallels between respiration and pigment metabolism. Copper, vitamin A, pregnenolone, progesterone, vitamin E and DHEA are intimately involved with both. The glucocorticoids tend to antagonize both.

Pigment Cells Related to Nerve Cells

Leghorn chickens are sometimes thought of as genetic albinos, but when relieved of the stress of egg laying, they can form black feather pigment. Domesticated animals of various kinds tend to become white. Soviet fox breeders selected foxes for tameness for 20 years. The foxes bred for tameness also lost their wild coloring, and became spotted.

The migration of pigment cells through the tissues of the developing embryo reflects in some way the altered balance of the whole organism.

It is this distribution of cells during embryonic and fetal development, and later in life, which produces "birth marks" and moles. Pigment cells and nerve cells are closely related in embryonic development, so it is interesting to notice the similar appearance of astrocytes in the brain and melanocytes in the skin.

Macrophages sometimes have a similar structure, and when stained with metals reticular macrophages and astrocytes (both have been called "metalophils") look surprisingly similar.

Metchnikov developed this theory of inflammation and immunity by phagocytosis in connection with his attempt to explain development, how ontogeny reflects—but alters—phylogeny. The recognition and preservation of self, in the immune reactions, was just an aspect of the ontogenetic creation of individuality.

When my phagocytes eat up one of my moles, and a good copy of my "original" mole is reconstituted in the same location, Metchnikov's idea of a dynamic organismic integrity, in which the phagocytes play a central developmental role, takes on new concreteness for me.

In 1983 I noticed that the whiskers on my cheeks were going white in circular as if the melanocytes were migrating centrifugally. Around the same time I noticed a flat mole, or raised freckle, was growing on my temple. Although many people have those spots removed, it is very common for people in their 80s to have a button-like black spot on the temple. My spot waxed and waned, but on average tended to get bigger and darker with the years.

In Mexico recently, a friend found that applying DHEA in vitamin E to a very big, red keloid tumor caused it to quickly fade and shrink. As I was driving home, I applied a little of the same solution to one of the mole on my temple. A day or two later I noticed a concentric ring of brown skin on the opposite side of the mole, about a centimeter away. The next day, there were two such bands. Then a bright red line appeared at the front margin of the mole, where I had first applied the oil. Although it looked as though the edge of the mole had bled, it was actually just a threadlike region of extremely dilated capillaries. Day by day, the thread of red appeared to be contracting around the mole. The brown rings took on a V-shape, and extended into the hair. The color of the mole became lighter for about a week, and as the red thread "contracted" the flat mole became pedunculated and mostly colorless, like a tiny mushroom. Two or three dots of color remained, apparently

trapped, in the globe. After drying and shrinking for a couple of days, it fell off, and the point of attachment had become smooth, normal skin within a day.

In this case, the concentric rings of brown pigment suggested that pigment cells might be returning to their normal locations, after having lived for ten years in an island on my temple. This might suggest that this particular skin area is the last to lose its ability to produce DHEA, and that well-nourished cells can remember where they belong.

Lipofuscin Produced in Oxygen Deprivation

Age pigment, lipofuscin, is produced in oxygen deprivation, apparently from reduced iron which attacks unsaturated fats. It has its own "respiratory" activity, acting as an NADH-oxidase. Melanin is produced by polymerization of amino acids, with copper as the catalyst. With aging, iron tends to replace copper. Melanin is an antioxidant. Thus, there is a sort of reciprocal relationship between the two types of pigment. A vitamin E deficiency relative to consumption of polyunsaturated fats, and an estrogen excess, accelerate the formation of lipofuscin.

A 47 year-old woman who had only a few "liver spots" on the backs of her hands began taking large amounts of estrogen, and within a few months the brown spots had darkened and spread until most of her skin was covered with spots. When she stopped using estrogen, and applied progesterone topically, the spots disappeared.

Since both keratinocytes ("keratinophages") and "melanophages" can phagocytize melanin granules,[2] the occasional rapid disappearance of "age pigment" makes me wonder whether pigment-loving cells can't ingest and destroy lipofuscin. To the extent that lipofuscin wastes oxygen, the phagocytes might be able to relieve some of the symptoms of oxygen deficiency in aging.

(My recent experience with an 82 year-old man with emphysema who regained a normal pink color a few days after beginning to use DHEA and pregnenolone led me to wonder whether the improvement was mainly in the lungs, or in the other tissues.)

If leukocytes can direct organized attacks on moles, with reconstruction of healthier tissue at the same location, the healing of an infection, or a wound, should be seen in the context of growth, construction, and creation, instead of simply attack upon a foreign body.

If leukocytes remove age pigments and deteriorated moles by recognition of an "age antigen," as in their removal of old red blood cells, or the unnecessary tadpole tail in maturing frogs, then we have a way to begin to grasp the mechanism of ontogenic evolution through various stages and "recapitulations of phylogeny," rejecting one structure as another step forward becomes possible. (The fact that the senescence antigen appears in embryonic kidney cells, as well as in adult liver cells, indicates that it has to do with development, the transition from one stage to another, rather than simply with the "wearing out" of cells.)

Melanoma sometimes spontaneously regresses, in a self-digesting manner.[3] This might be the process that I have seen in my "autolytic" moles. The fact that the "tumor necrosis factor" is also a cachexia inducing factor (and is produced by activated macrophages) provides another perspective on the idea that the whole body might be designed to periodically melt-down, to be systematically reconstructed anew.

Mortality Again

Townsend Letter for Doctors, June, 1994

MARIA de Sousa's work on thymus-derived cells and their relation to the body's iron economy has made people aware of the possibility that iron "fortified" flour and other foods might be contributing to the incidence of leukemia and other cancers, and to immunodeficiency resulting from maldistribution of lymphocytes.

"And with the weight of iron advertisements in this country one inevitably starts feeling that it is not going to be easy to tell this community that in some circumstances iron may be bad."

"It is iron and Flintstones, and the food almost all of our Hodgkin's children ate—as we found out from the rough survey of eating, drinking, and living habits."[1]

It was probably the World Health Organization's observation of a high death rate from malaria in people who were given supplementary iron for their "anemia" that made it obvious that iron can have rapid and deadly immunosuppressive effects, though it had long been suspected that an increase in the iron burden was a factor in the immunosuppressive action of blood transfusions. My interest in the toxicity of iron was aroused by the published discovery that, when added to animal food, iron destroys the vitamin E which was also added to the food. Subsequently, it was found to destroy other vitamins, too.

In recent years, the interaction of iron with vitamin C (and other reductants) and unsaturated fats, to produce lipid peroxidation, has been the dominant issue in research on the toxic effects of iron. "Reperfusion injury," any stress causing oxygen depletion and an excessively reduced (electron-rich) cellular state, the importance of lipid peroxidation and iron in aging, and the role of iron in damaging steroid synthesis in steroidogenic tissues, have been important lines of study lately.

Early in the century, the tendency of calcium and iron to be deposited together in damaged tissues was noted, but the exact reason for this association still isn't known. I think iron's role in "age pigment," lipofuscin, is an important part of the mechanism. In oxygen deprivation, heme (the iron-binding oily component of hemoglobin and various enzymes) is produced, largely by spontaneous, non-enzymic means. Age pigment consists mainly of lipid peroxidation products, with heme and iron. It

has the adaptive function of keeping NADH oxidized in a low-oxygen environment, in which mitochondrial respiration is inadequate, allowing NADH to keep the glycolytic sequence operating. It has been found that age pigment is produced in the fetus, because of its low-oxygen environment, and in fish that are living under ice, again because of the low-oxygen environment, which allows iron to become reduced and to catalyze lipid peroxidation. In old age, blood leaving the lungs is often only half saturated with oxygen; the tissues are likely to be overloaded with iron, and it becomes increasingly likely that fat will be mobilized as an energy source.

The other factors besides iron overload and oxygen deprivation which cause premature loading of the tissues with "age pigment" are a diet low in vitamin E and/or high in unsaturated fats, and an excess of estrogen.

Around the time these factors in the formation of age pigment were being investigated, the Shutes were investigating the antagonism between estrogen and vitamin E. Essentially, their antagonism consists of the fact that vitamin E spares oxygen, and that estrogen wastes oxygen.

Women absorb dietary iron about three times as well as men do, but during pregnancy their absorption is about nine times as efficient as men's.

The famous antagonism of molybdenum to copper absorption is similar to that between iron and copper. Copper deficient cells, for example in the heart, become overloaded with iron. Recently, various studies[2] show that cellular oxidative stress promotes iron retention, which would be logical, since iron is essential for respiration, and cells struggling to respire would tend to use evolved mechanisms for retaining the iron needed to form new respiratory enzymes. (As I suggested above, I think spontaneously formed heme is the probable reason for iron's tendency to concentrate in hypoxic tissue.) Estrogen, by creating relative hypoxia, promotes iron retention.

The fetus, a whole organism within an organism, has a special oxygen problem. Fetal hemoglobin, with a great affinity for oxygen, helps it survive in that situation. (I suspect that fetal hemoglobin will reappear whenever there is prolonged hypoxia.)

I believe it is the low oxygen environment which causes the fetus to be born with a great surplus of iron. Prenatally, iron is absorbed about 40 times faster than while the baby is nursing. Although pregnant women absorb iron from food very efficiently, they tend to give up their stored

iron to the baby. This could account for the greater longevity associated with having more babies, and especially with the lower incidence of cancer in child-bearing women.

Milk is remarkably "deficient" in iron, and it seems obvious that this is an adaptive feature, allowing the child to "grow into" the large amount of iron stored in its tissues at birth. I mentioned the fact that iron and calcium both tend to be deposited in damaged and dying tissues. If it is the situational hypoxia of the fetus that causes its prenatal iron overload, we might expect it to be "overloaded" with calcium, too, and that seems to be the case, with the extra calcium being stored in the porous centers of the bones.

Estrogen causes an exaggerated absorption of calcium, as it does of iron, and high calcium diets have been found to be very toxic to pregnant animals. The combination of estrogen and calcium can cause a condition called osteopetrosis, or hardening of the bones, in which the bone-marrow cavity is closed up, severely limiting the production of the cells which would become Natural Killer cells, normally found in the spleen. Estrogen causes a reduction of Natural Killer cells in the spleen, even without destruction of the bone marrow.[3,4]

Estrogen, and a variety of poisons, cause even soft tissues to retain calcium. It is clear that scleroderma, a hardening of the skin, involves the interaction of calcium, iron, lipid peroxidation, and hormones, but lately it

seems that no one wants to think about it physiologically. The food and drug industries have their motives; we are hearing more about drugs to chelate iron and calcium from the body, than about simply leaving iron out of food, or restoring vitamin E and magnesium. And researchers like to aggrandize themselves by making problems seem more complex than they really are. And of course, disease-centered fund-raising organizations always see their business as raising funds, not finding cheap solutions to problems.

At the age of 12, people are less likely to die than at any other age. The curves for mortality from cancer, and from all causes combined, are similarly shaped, with a minimum around the age of 12. The sex hormones tend to stop bone growth, at least in the sense that puberty leads to the hardening of the growth-areas of long bones. When growth stops, the concentration of iron in the tissues tends to increase (even without considering the effect of hormones on iron absorption).

The high mortality of old age is associated with a high concentration of iron in the tissues, just as the high mortality of young infants is associated with a high concentration of iron. As the infant's iron is diluted by growth, mortality decreases.

Infectious disease and leukemia, which have been associated with excess iron, are highest in childhood and old age.

June Goodfield's book gives a nice summing up of the early research on the relation of iron metabolism to cancer and immunodeficiency:

"...in essence the immunological system has evolved with the ability to survey, and recognize, and utilize—I don't know exactly what. But this ability is expressed as a capacity to survey metals and, in particular, iron."

"It goes in as ferrous iron, and is then rapidly oxidized into ferric iron. This is then bound to a protein, transferrin, and so is carried into the bone marrow and thus given to the early red blood cells, which need it for the blood cycles. But iron is also bound to a second protein, ferritin, which is a storage protein...When red cells get old they break down in the spleen and are eaten up by the macrophages, which then make ferritin. (It enters the storage pool again.) Then there is the third protein, lactoferrin, which is synthesized by polymorphs, the white cells, and is present in milk and in our secretions. The amount we excrete per day is absolutely minimal. You can only shove it in; you can't push it out. Now if, for some reason or other, there is too much iron around, the macrophages go and mop it up. And as far as I'm concerned, in the diseases we've been studying—Hodgkin's, leukemias—there is an abnormality in the lymph nodes and the macrophages in regard to the intake, or the handling, of the iron...I have a simple scheme, again probably too simple. Lymphocytes go and are caught where there is an excess of iron. A malignant cell, like a virulent cell, behaves like a virulent bacterium. It becomes capable of sucking up iron avidly and utilizing it...if the tumor cells eat up the signal—iron—the lymphocytes won't go there. The tumor will grow undisturbed because the lymphocytes have not had a signal to move toward it."

As I mentioned above, I think some of the excess iron accumulates in the form of age-pigment, and that this material serves to keep glycolysis running as an emergency energy source. Glycolysis produces lactic acid, which is characteristic of tumor metabolism even in the presence of oxygen, and lactic acid has its own direct effects on immunity.

Americans who eat processed grain products are obliged to eat iron, because of the federal law that they must be "fortified," in spite of the clear evidence that adding iron to food destroys its vitamins. Only public pressure can change this law. Those who have promoted the use of iron fear change, because of their potential liability.

Natural Immunity and Viral Infections

Townsend Letter for Doctors, August/September, 1988

W. F. Koch worked in Moses Gomberg's lab, where free radicals were first observed. Koch soon constructed a theory of natural immunity against virus and cancer, based on his belief in the existence of biological free radicals, able to oxidize virus particles and carcinogenic molecules. Koch believed that allergies were an early sign of the failure of this free radical oxidation system.[1,2]

Albert Szent-Györgyi worked out some of Koch's ideas, and in the process discovered vitamin C (which has a free radical state), and explored many other energy exchange processes, including free radical activation by biological pigments.[3]

Both of these men argued that there is a special interaction between biological structure and the activated electronic state, and that both structural and electronic properties of molecules are involved in their toxic or therapeutic functions.

This model of cell structure and function leads to the expectation that any substance is likely to have a broad range of effects, acting on many different cell types, and promoting or suppressing cell functions, depending on the cell's type and its present state.

In this view, the living material is not an ordinary liquid, but is deeply structured, somewhat like a liquid crystal, and this structure is subject to many physical influences, in the process of adapting to a changing environment.[4]

Newer techniques are letting us visualize more of this finely structured cellular system, and it has been found that many types of virus replicate themselves while attached to the cell mesh-work.[5] Alterations in the mesh-work and the adjoining water will obviously affect the ability of the virus to multiply.

The highest energy states of the cell tend to exclude water soluble substances, and to absorb oil soluble materials. The components of a virus have very specific affinities for water and oil, and they can be assembled only in a very special solvent environment. As mentioned above, a substance which modifies any type of cell will modify others. The high energy state of a cell is an electrically "hyperpolarized" state, and for a nerve cell this is an inhibited, quiet state.

Camphor

There is a long history of anesthetic substances being used to treat viral diseases. Abrams, in a 1910 textbook, described the use of chloroform to cure a viral disease in a horse. Camphor, besides being used as a local anesthetic and a heart stimulant, has been used to treat influenza and other systemic diseases,[6,7] and is one of the oldest topical treatments for herpes sores. More recently, a veterinarian reported curing an "incurable" virus disease in a dog with an anesthetic dose of ether.

Adamantane, which can be extracted from petroleum, is a close structural analog of camphor, and smells like camphor. With the addition of a nitrogen atom, it is water soluble, and is an effective anti-viral agent, and is also widely used in treating Parkinson's disease (its function is cholinolytic),[8] and more recently is being used in preventing withdrawal symptoms in cocaine addiction.[9] It is not metabolized, and does not present the genetic risk that has recently been recognized for other anti-viral agents which disrupt viral DNA.[10]

The fact that the body is well supplied with substances which—at a slightly higher concentration—are anesthetics, and which are depleted by the stresses which predispose to viral infections, suggests that they may normally have a camphor-like anti-viral activity. Some of these substances, the anesthetic steroids, have been found to prevent some viral infections,[11] and they also have a wide range of anti-toxic effects.[12] Pregnenolone, progesterone, DHEA, and pregnanediol are all good candidates as anti-viral drugs, but etiocholanolone—which also produces fever[13]—is the most interesting of the group.

It is well-known that stress, acting mainly through the glucocorticoid hormones, damages immunity by destroying thymus cells. The anesthetic steroids, especially progesterone, normally reduce the need for secretion of cortisol, but also act as a protective buffer against the damaging effects of cortisol.

Although a physiologically balanced amount of cortisol induces enzymes of detoxification, for example in the intestine, an unopposed excess causes destruction of these enzymes, eliminating much of the intestine's barrier function, and leading to allergies.[14] This action of cortisol against the thymus and against the bowel's detoxifying enzymes very likely accounts for the common association of allergies with virus infections. Since cortisol has a destabilizing, pro-convulsant effect on the

nervous system, there are likely to be psychological symptoms—anything from compulsive behavior to depression or seizures—associated with the other chronic conditions.

In the last century, it was observed that digitoxin (a natural steroid derivative) lowered the fever caused by enteritis.[15,16] This is probably another example of a catatoxic function, a protective function common to many steroids, and probably worked by way of stabilizing the detoxifying enzymes and preventing the absorption of endotoxin.[16] Endotoxin is known to destabilize and inactivate the bowel's detoxifying enzymes, just as an overdose of cortisol does.[17]

Biological Erasers

Although it is important to be aware of the deadly effects of chronic, unopposed exposure to cortisol (and estrogen and prolactin), these hormones which cause atrophy and loss of function in various tissues also have a creative function. I have elsewhere called them the biological "erasers," the hormones of new beginnings.[18] In the case of cortisol, it might be useful to compare its effects on tissue cells to the process of winnowing wheat, in which the chaff is blown away while the grain is retained. I think there is a mechanism, as proposed by Meerson, in which a functional load preserves the cells and systems which are needed in the present environment, while idle cells are eliminated or reduced by cortisol's catabolic action.[19] In this view, intermittent exposure to these hormones would improve resistance, but continuing uninterrupted exposure will destroy resistance.

Adequate energy, for example as available glucose, is protective against cortisol-induced catabolism. White blood cells can protect themselves by metabolizing cortisol in the presence of sufficient glucose.[20]

Some of the consequences of stress are not catabolic. When the detoxifying enzymes have been lost, then bowel toxins block other basic enzyme systems, leading for example to slowed protein turnover[21] and decreased activity of superoxide dismutase.[22] The consequent increase of lipid peroxidation will decrease steroid synthesis.[23] Stress also leads to the production of intracellular toxins, including ammonia and carbon monoxide, which tend to perpetuate the blocked state.

Just as with the anesthetic substances which modify the physical state of the cell, retarding viral replication, the oxidative protective

system has several points at which intervention is possible to support detoxification, and to promote protein turnover.

Injecting Enzymes

Although natural promotion of the enzymes which degrade proteins and nucleic acids will help to shift the equilibrium away from virus production, recent research shows that it can be therapeutic to inject enzymes (nucleases, both DNAase and RNAase) which degrade viral nucleic acids.[24] Using labelled enzymes, it has been demonstrated that virus and enzyme can enter the cytoplasm in the same vesicle. In herpetic keratitis, the enzyme is used as drops and also injected under the conjunctiva, and in infectious mononucleosis and viral encephalitis it is injected intramuscularly.[24] In treating a viral paralysis of bees, the enzyme is administered as an aerosol. It was found that treatment increased the viability and productivity of outwardly healthy bees, apparently by curing a latent viral infection.[24]

While W. F. Koch was interested in the body's own oxidative free radical system of destroying toxins and pathogens, he studied several natural quinones found in medicinal plants. Recent work has found that phototoxins extracted from plants can kill mouse-cytomegalovirus without damaging the mouse cells.[25] These researchers selected chemicals which do not disrupt genetic material, recognizing the probability of serious side effects.

Although injected enzymes and plant toxins are safer than some current chemotherapies, the basic approach to controlling viral diseases should be to support natural immunity, by maintaining energy production at a high level, by unblocking and stabilizing the detoxifying enzymes, including mono-oxygenases, proteolytic enzymes, SOD, and nucleases, and by avoiding prolonged catabolic states. Many natural substances are available which promote these ends, without risk.

While this approach supports the known mechanism of the immune system, including protection of thymus cells and activation of the various white cell mechanisms of attack, it has the novel feature of altering cells physically to retard viral assembly, increasing their exposure to nucleases, proteases, and mono-oxygenases; that is, it mobilizes immune processes in cells which are not part of the immune system. By eliminating stress-induced susceptibility, it systematically shifts the balance toward

normal functioning, and away from parasitic diversion of the organism's resources.

Negation

Vision and Acceptance, January 22, 2014

THERE is one concept that has altered my perception of life more than anything I have ever studied. Some people know it as "negation" others as "denial." I have some ideas for future blog posts where I plan on referencing this theme more directly. Before that can happen, I feel negation needs to be explored and contemplated on its own with as little distraction as possible.

For some of you, this may be an introduction to the idea and I take this seriously. So I called in the big guns, someone who has studied the matter much longer than I have and has helped me to deepen my comprehension of it. I present the following to you, Dr. Ray Peat on Negation:

I think the concept is very simple in itself, but the problem is that it implies a cultural criticism that involves everything, biology, physics, politics, epistemology. Contraries, or different perspectives, can interact to eliminate error, in progressing. Negation is a human function that would stop the free advance of life and consciousness, opposing critical questioning and spontaneous understanding. The refusal to discuss a problem, and the many forms of censorship, and legal-economic systems that make whole courses of action impossible, are negations, that have their poisonous effects. Physiology reflects their poison, in all the ramifications of learned helplessness, restraint stress, the carcinogenic effects of work-school-media-religion-government.

Negation excludes or suppresses those complex processes of being, and implants nothing but—at the most—obligation in their place. Undocumented aliens are negated simply, slaves and citizens are negated but with obligations. Religions tell people that their being is immaterial, a ghost that will be o.k. somewhere else forever, if they do their duty now. Having a false consciousness implanted by schools and television, labels and roles take the place of being. A sense of despair and impossibility is right behind the false consciousness.

Our surrounding context of language and culture is constantly distorting and misinterpreting anything which persists in moving toward a more expansive life. Knowledge, a physiological thing, is expansion,

and as such is always clearing away errors; when people identify with error, they see knowledge as the deadly enemy, that must be destroyed.

Blake's idea of the "intellectual fountain" was very different from the attitude of Schopenhauer and Nietzsche (where "Will" or assertion was the fundamental reality). Blake saw it as always flowing into new territory, discovering new things, enlivening the world that's being discovered-created. When the organism is traumatized, it hardens, and stops developing, and wants to impose its moral hardness everywhere; assertiveness is the antithesis of perceptive life, and devises ways to negate it.

In an authoritarian culture, people want you to forget who you are, so they can implant themselves without resistance. Just recognizing your own presence, to attend to them fully, is something they don't expect; it isn't quite like Carl Rogers' therapeutic presence, because it's conditional—your conscious presence is the condition. Being present and able to listen (and question and understand) is receptive and productive, and it can even be disruptive, but it's very different from being assertive, because it's always hoping to open up new possibilities, rather than imposing something carried along from the past. A priest is being assertive when he says you have to take it on faith, a physics professor is being assertive when he won't justify his assumptions—where would physics be if your assumptions had to be plausible beyond a particular culture of physics? Much of their potential imagination has been invested in thinking of ways to keep you from questioning.

Physics, in the 20th century, has taken on the Nietzchean subjectivism, claiming to quantize/digitize everything. There is no digital nature, but assertive subjectivism has effectively written quantization into the constitution of science, and into the shadow of the humanities that remains in the corporate universities. Bits of "knowledge" are sold and hoarded, and people who would show that they are something other than knowledge are treated as vandals and worse—Aaron Swartz, for example.

A Little Boy Lost

> Nought loves another as itself, Nor venerates another so, Nor
> is it possible to thought A greater than itself to know.

'And, father, how can I love you Or any of my brothers more?
I love you like the little bird That picks up crumbs around the door.'

The Priest sat by and heard the child; In trembling zeal he seized his hair, He led him by his little coat, And all admired the priestly care.

And standing on the altar high, 'Lo, what a fiend is here! said he: 'One who sets reason up for judge Of our most holy mystery.'

The weeping child could not be heard, The weeping parents wept in vain: They stripped him to his little shirt, And bound him in an iron chain,

And burned him in a holy place Where many had been burned before; The weeping parents wept in vain. Are such thing done on Albion's shore?

A Poison Tree

I was angry with my friend: I told my wrath, my wrath did end. I was angry with my foe: I told it not, my wrath did grow.

And I watered it in fears, Night and morning with my tears; And I sunned it with smiles, And with soft deceitful wiles.

And it grew both day and night, Till it bore an apple bright. And my foe beheld it shine. And he knew that it was mine,

And into my garden stole When the night had veiled the pole; In the morning glad I see My foe outstretched beneath the tree.

Introduction

Hear the voice of the Bard! Who Present, Past, & Future sees Whose ears have heard, The Holy Word, That walk'd among the ancient trees.

Calling the lapsed Soul And weeping in the evening dew: That might controll. The starry pole; And fallen fallen light renew!

O Earth O Earth return! Arise from out the dewy grass; Night is worn. And the morn Rises from the slumberous mass.

Turn away no more: Why wilt thou turn away The starry floor The watry shore Is giv'n thee till the break of day.

The Voice of the Ancient Bard

Youth of delight come hither. And see the opening morn, Image of truth new born. Doubt is fled & clouds of reason Dark disputes & artful teazing. Folly is an endless maze, Tangled roots perplex her ways. How many have fallen there! They stumble all night over bones of the dead And feel they know not what but care; And wish to lead others when they should be led.

Neutrinos and Long-Range Interactions

Multidisciplinary Research, 1976

WHAT'S implied by "a wave"? Something which undulates, ripples, or waves—something which persists, and undergoes a change which is transitory, but a change in shape and energy which extends both through space and through time. We can perceive such movement because our senses operate with some intrinsic generality. If the action of rippling water is reduced to a series of sets of points, it is meaningless until we restore the wholeness and generality which encompasses those points.

To have a "wave without a medium," as most contemporary physicists believe they must, means to them that we must suspend our materialistic common sense, and believe in an abstract reality. They neglect the possibility that the extension through space, the spatial interactions, might be a property of matter interacting with the light, and they deny the other major possibility, that light could be waves in a medium which fills space. I want to suggest that both of these processes may be operating to different degrees, depending on material conditions.

In place of a medium, the physicists have come to believe in "fields," mathematical expressions of forces, which ultimately exist as distortions of the geometry of space. So they present us with a space which really exists, so that it can have a geometry and be distorted, but which has no properties other than those introduced into it by things and their forces. Waves of "gravity," for example, will influence geometry in a way so that things will move toward each other—they are like signals, indicating to the other object how it should behave. Although most physicists have a perverse love for abstractness, for mathematizing the world and making space into a formal but empty something, this scheme of a space with no properties is potentially fruitful, if we use it only as a starting point to free us of the formalisms of Cartesian and Leibnizian space and time, and if we immediately start filling it up with what we need to account for observed interactions of things.

Some of Reich's apparently most muddled comments about light (e.g., "If 'light' is due to local orgone lumination and does not 'travel through space' at all, it is quite understandable that in the Michelson experiment no phase difference could be observed in the light beams

which were 'sent' in the direction of the ether 'drag' and perpendicular to it") seem to have been intelligent attempts to describe physically what he could directly perceive about the nature of consciousness and perception itself: that it is a "lumination" of the living material in resonance with a "lumination" in the world beyond the organism. A "chemical" illustration of this process is the "resonance of electrons" which makes some molecules act as an electronic unity, rather than as a cluster of individual atoms stuck together.

Bandyopadhyay and Chaudhuri (1971) have described how gravity can be accounted for on the basis of charged particles tending to move into a region where the dielectric constant is greater, by assuming that the dielectric, the "neutrino sea," tends to be associated with matter. A similar effect has been used to separate living cells from dead ones—in pure water, living cells with a high dielectric constant will move toward a concentration of charge. This experiment, incidentally, shows a dielectric moving on a charge gradient and suggests how the neutrino sea would tend to be concentrated around matter. If the "ether" is in fact a "neutrino sea," as Dudley has argued, then this is a very important property: it would not only be "dragged along" with the earth, but its density would change according to the density of ordinary matter in that region, and this would resolve the question of whether Reich's orgone accumulator was a Tesla box which accumulated electrons, or an orgone accumulator—charge would concentrate neutrinos, and vice versa.

It has occurred to me to wonder how quickly this association can be formed: for example, could a lense escape its concentration of ether by moving very rapidly? According to Dudley, the neutrino sea is isotropic, with neutrinos moving at various velocities up to their maximum, which may be the speed of light; if this is so, then maybe some of the slower neutrinos could be escaped from at high speed, like running thru a swarm of annoyed bees.[†] Presumably, a lense's refractive index could be changed slightly by putting it in different environments or by moving it at high speeds. If the field of neutrino concentration reacts quickly, then a kind of mechanical resonance between objects should be possible, in which vibration could be transmitted by fluctuations in the neutrino gradient. Dudley's suggestion that phonons and rotons can interact with the neutrino sea would also imply the possibility of mechanical resonance directly through the ether. Charge oscillations would also presumably cause oscillations of the dielectric medium, the neutrino sea.

At first this seems to be an excessively peculiar idea, and it may seem better just to think of purely electrical interactions, as in the London forces, with electronic fluctuations or protonic fluctuations (Kirkwood). Phonon-electron interactions, for example, are certainly conceivable without assuming an oscillating medium. But it may be that there are "resonant interactions" which don't involve ordinary sound or electromagnetic processes. A fairly large neutrino "resonant domain" in a metal could, for example, absorb waves of radiation in a way consistent with the photoelectric effect.

Reich's observations of lumination in evacuated tubes might result from a process like this: in a corona discharge, air molecules are ionized, and emit light on recombination: in the dielectric, water, salts become highly ionized; high fluxes of neutrinos might provide the dielectric conditions which promote ionization of the gas molecule in the tube, with light caused by recombination. (This is a matter of shifted equilibrium and not of energy—thermal energy, for example, can be adequate. The neutrinos, etc., might provide the energy.)

Some Russians have proposed that the forces involved in psycho-kinesis may be related to gravity, and that these forces may be what makes life possible, and that they may constitute the material form of mental activity. Drs. A. P. Dubrov and V. N. Pushkin are among those who think something like gravity is involved in psycho-kinesis. The people who have been studied in the USSR move things somewhat as if they had a static electrical charge on their hands, but that has been eliminated as the responsible force; one man presses a book between his hands, gradually removes his hands, and keeps the book suspended. Uri Geller, who performs on U.S. television, says he thinks he is directing some kind of energy outside of his body—his most interesting act is bending nails and keys. These various kinds of psycho-kinesis all are consistent with Dudley's postulations regarding the neutrino sea. Also, Uri Geller's in particular recalls Michael Polanyi's studies of bending and breaking forces in metals and crystals; Polanyi explicitly proposed an "excitable ether" in connection with other observations, but nearly all of

† If it takes time to establish resonance, this would happen—but if neutrinos are caught as easily as outrun, there would be no effect. And if force is exerted by the charged matter on the neutrinos, they would no longer be part of the sea, but would be part of that particular material system. (A slight excitation might be the closest kind of coupling between atoms and ether.)

this scientific work was in the field of "long range interactions"—friction, adsorption, breaking, and reaction rates, for example, were studied in ways which revealed the inadequacy of the conventional "crystal lattice" and "atom to atom" ideas of interaction.

If we hold the mystical-mechanist world-view of conventional physics, things like psycho-kinesis have to be subsumed under "conspiracy" or "delusion." Enough people have seen the performances of Boris Yermolayev, Uri Geller, et al., that a theory of "conspiracy and delusion" now has to be treated as a "lunatic fringe" idea.

In outline, the biophysics of neutrinos might be something like this: biological water, being uniquely ordered, could provide extensive systems of "resonant domains" of interaction with the neutrino sea; these crystalline regions would tend to be mutually stabilizing through resonance with each other, the co-ordination might include electronic and electromagnetic interaction, accounting for the tissue "lasing" apparently involved in the observations of Gurwitsch and others; special interactions between organisms and neutrinos should be measurable in various ways, and might account for the "time" effects of N. A. Kozrev, Reich's lumination and many other of his effects, and maybe for the loss of weight that has been observed at the moment of death by various investigators (however, it also seems that loss of order in cellular water would reduce solubility of gases, and cause a measurable weight loss from gas emission at death). If the organism is seen as a kind of lens or pump for the ether, the neutrino sea, then special cases of its interaction would be expected to involve anything which normally depends on "ether excitation": reaction rates, metal bending or breaking, adsorption, crystallization, and nuclear reactions are some processes suggested by the work of Polanyi and Dudley. The effects of "healers" hands on enzyme rates might be a case of this that is already well known. I think there have also been claims about mental effects on crystallization and nuclear fission.

If consciousness itself importantly involves the neutrino sea, then the ether could be an additional channel for perception and communication, that is, a channel for direct resonance between the organism and what it perceives.

On Recycling Placentas, Thyroid Suppression, and Carpal Tunnel

Townsend Letter for Doctors, August/September, 1990

I am glad to see your comment, "Recycling Placentas," in the June issue. More such dialogue between authors and editors could make the magazine more interesting. Last month, I decided to wait to see whether others would comment on Musarella's statements. Since your comments covered many of the points that needed to be made, I'd just like to add some of my other reactions.

Usually, the authors of foolish medical claims at least have the slight virtue of pushing common errors to an absurd extreme, helping to make thoughtful people more conscious of a problem they hadn't been paying attention to. But there are suggestions in Musarella's article that threaten to besmirch good research. I don't know what "Pr." might stand for, but Filatov is grammatically masculine (Filatova would be a woman's name), and in Russian medicine, the phrase "the Russian scientist Filatov" would be assumed to refer to Vladimir Filatov, after whom at least one Filatov Institute has been named. Vladimir Filatov was a pioneer in reconstructive surgery and in corneal transplants from cadavers. He found that corneas transplanted from cadavers that had been kept in cold storage for some time exerted a healing influence on adjacent tissues. He saw similar effects in reconstructive surgery using "tube-flaps" of skin, and concluded that tissues subjected to stressful conditions formed substances which promoted healing and regeneration. (Succinic acid and other dicarboxylic acids were identified among the "biogenic tissue stimulators." Succinate stimulates respiration and steroid formation, and protects against peroxidative damage. Filatov's work is an important complement to that of Engelhardt and Szent-Györgyi and Polezhaev and Meerson.) Because abscesses often formed when vital tissue was implanted, Filatov tried sterilized tissue, and found that it was as effective in stimulating healing and regeneration. At this point he realized that tissue extracts would have the same effects, and he made and used extracts from a great variety of "stressed tissues," including leaves. He published results showing that sterile extracts could stimulate regeneration of the optic nerve, and of various other tissues. Many years after he died, people

at the Filatov Institute found that extracts of placentas were extremely beneficial to old people.

If there is a New Filatov who rejects the conclusions of Vladimir Filatov, and uses vital placental tissue, in a caricature of the experiments at the Filatov Institute, Paul Musarella certainly owes us an explanation, because his phrase, "the Russian scientist Filatov" is misleading. But I think Musarella is more likely just another person exploiting the gullible public, who are justifiably impatient with the failure of the medical establishment to work seriously on problems of aging and regeneration.

Although the *Townsend Letter for Doctors* deliberately avoids filtering out crazy ideas, I think a tiny editorial note at the end of such articles would be appropriate, commenting for example that no references were submitted, that the identity of "Pr. Filatov" wasn't explained, and possibly giving a little more information about the author.

Oral Absorption of Progesterone

JAMA, Volume 78, Number 3, 1986

SINCE many synthetic progestins are known to be luteolytic,[1] and while progesterone itself exerts a served in previous cycles, but in some women the effective dose caused the blood levels to rise somewhat above the levels usually considered normal for the luteal phase.

Postmenopausal women, who have much lower average levels of estrogen and who produce little progesterone, show much more clearly the effects of administered progesterone. Seven women who had gone through "natural" menopause at least two years previously, and whose serum progesterone was either below the sensitivity limit of the competitive protein-binding technique or in the typically low postmenopausal range of measurement by radioimmunoassay, were given oral doses of 50 mg or 100 mg of progesterone in tocopherol.

The earliest any blood was drawn after an oral dose of progesterone was 20 min; in this case, the progesterone had risen from 0.2 ng/mL before to 0.7 ng/mL after a dose of 100 mg.

When blood was drawn from 4 h to 8 h after an oral dose of 50 mg to 100 mg, the blood levels were between 6 ng/mL to 16 ng/mL. No attempt was made to assure that the progesterone was taken on an empty stomach; meals were eaten as usual while waiting for blood to be drawn. The progesterone was administered by the women's physicians, and the measurement was done by commercial medical laboratories.

In two cases in which blood was drawn 24 h after a single dose of 100 mg, the progesterone level was still in the normal luteal phase range.

Since the observations were made over a period of several years, with progesterone measurements made at several different laboratories by different techniques, the numbers are not strictly comparable. We recently got a clearer picture of the rate of absorption in a fasting person. A middle-aged man, with a fasting level of 0.2 ng/mL took 100 mg. At the first hour, the progesterone level was already 7 ng/mL; the concentration rose each hour to a peak at the sixth hour of 14 ng/mL, and the last measurement, at the seventh hour, was 0.2 ng/mL. On average, men's livers are quicker to remove substances from the blood, and the fact that no food was taken during the test very likely caused the rate of increase and the rate of decrease to be greater than in a nonfasting person.

In summary, when dissolved in tocopherol, progesterone is orally active. A single oral dose of 50 mg to 200 mg given to women with luteal phase insufficiency or to postmenopausal women brings their blood progesterone levels up to at least the normal luteal phase range and maintains it in that range for at least 12 h.

Oral Progesterone is Not Inactivated by Stomach Acids, Pancreatic Enzymes or Liver Detoxification

Townsend Letter for Doctors, February/March, 1995

STEPHEN Dentali, commenting on my remarks about oral progesterone, has indicated that "any pharmaceutical text" can be consulted to understand certain issues in pharmacology and pharmaceutics.

Textbooks are useful for introducing students to a new subject, and they are an interesting literary genre, allowing us to see how the individual author handles a certain area of knowledge. But anyone who has seriously studied a subject knows that textbooks aren't intended to resolve scientific questions. Different authors sometimes take different positions on the issues.

By reading many texts on a given subject, we can see that the people who write textbooks are usually far behind the decisive scientific work in most of the areas covered by their book. If they are researchers themselves, their particular area will usually be described in an up-to-date, though personally filtered, manner. Increasingly, publishers are influencing the content of textbooks, for the purpose of maximizing sales. (Richard Feynman's entertaining discussion of textbooks should be read by every teacher.)

It is important to critically examine original scientific publications, but textbooks are generally so far removed from the original work that it would be a waste of time to criticize their subjectivity and inaccuracy page by page. That isn't necessary, as long as people realize that they shouldn't be treated as anything but secondary (or tertiary) sources.

Many textbooks have said that since insulin is a protein, and since proteins are digested in the stomach, insulin is inactive when taken orally. Since oral insulin can cause lethal hypoglycemia in dogs (whose capacity to digest protein is very great), we can see the limitation of reasoning without evidence.

Progesterone happens to be very resistant to acid as well as to stomach enzymes, but ultimately the body is able to modify it into other substances, which are excreted.

Dentali invokes the "first pass" dogma of liver inactivation, but he neglects the whole point of what I said, namely, that chylomicrons are not consumed on the first pass though the liver. Progesterone equilibrates

from the chylomicrons into the other fractions of the blood, and a large part of it is carried in the red blood cells. Laboratories which measure the progesterone (or pregnenolone, or DHEA) contained in the serum after removing the chylomicrons and red blood cells are probably following some old textbook dogma, without realizing that they have discarded a major part of the hormone they would like to measure.

Dentali seems to have been offended by my reference to the "bizarre crystallization" that occurs in some progesterone products, and by my reference to FDA errors. I will respond to those points.

If the products that are unstable oily solutions bore labels warning users to heat and stir the mixture before use, they might be acceptable. But some of the products are in opaque bottles, and the physicians who prescribe them are not likely to suspect that the progesterone crystals have settled to the bottom. My patent is based on the fact that vitamin E stably holds progesterone in solution, so that it can be assimilated effectively by any route, transdermally, vaginally, or orally. Various companies have tried to take advantage of the awareness that my formula works, but I think some people have assumed that any product which contains "vitamin E" and progesterone will work in the way I have described. In the case of opaque transdermal (or rectal or vaginal) creams, the progesterone crystals in bad formulations are harder to see.

Spreading the cream in a thin film, they can be seen under a microscope. What is visible is not going to be able to go though the skin.

FDA officials have said that the only "approved" form of progesterone is the oily injectable form, which is described as progesterone dissolved in vegetable oil, with benzyl alcohol added as a bacteriostat. In "bacteriostatic water," benzyl alcohol may be present at 0.9 % to 1.9 %, and even at that concentration it is a dangerous neurotoxin and allergen. But the vegetable oil used as vehicle is a very poor solvent for progesterone, and it is not a hospitable environment for bacterial growth. (For example, it is a strong mutagen.) The so-called progesterone in vegetable oil needs the very high concentration of approximately 10 % benzyl alcohol to stay in solution on the shelf. When such a solution is injected, the toxic alcohol diffuses away into the body fluids, leaving the (cancer promoting) vegetable oil with progesterone, and the progesterone crystallizes out of solution. The benzyl alcohol is the actual solvent that permits the progesterone to stay in solution while the product is on the shelf. The massive amount of this neurotoxin in the

"approved" form of progesterone is reminiscent of the FDA's approval of a bronchodilator for asthma patients which contained metabisulfite as a preservative. When I told them that I thought that was an irrational product, since metabisulfite can kill people with asthma, and that the deadly "paradoxical" bronchoconstriction that was killing patients didn't seem paradoxical at all, they just didn't respond in any visible way. They similarly have not responded to the many complaints I have made about their "approved" form of progesterone. In another case, when I sent them evidence of what I believe is a gigantic and continuing drug fraud, they actually wrote me a letter saying they don't handle individual's complaints.

The FDA has done tremendous damage to women's health by claiming that natural progesterone has the terrible side effects of the synthetic progestins. This has never been a scientific issue: It is strictly a matter of the FDA's giving demonstrably false information to the public. Some of the widely used synthetic progestins have been powerfully estrogenic and teratogenic, while natural progesterone is neither.

Natural progesterone is known to be a safe and effective treatment for epilepsy, while all the recognized anti-seizure drugs are teratogenic, and it is largely the FDA's false attribution to progesterone of the side-effects of synthetic progestins that is responsible for the continued failure to make progesterone available to pregnant women with epilepsy.

Progesterone can be used as an anesthetic, but it is not correct to ascribe to it the properties of ether.

Progesterone has anti-inflammatory properties, but it is not correct to say that it must therefore have the properties of cortisol.

Progesterone has mineral-regulating properties, but it is wrong to classify it as a mineralocorticoid.

Long ago, Hans Selye pointed out some of the problems involved in classifying multiple action substances by one of their actions. But what the FDA has done goes far beyond any problem with sloppy scientific terminology. It has falsely claimed that the toxic properties of various synthetic drugs belong to natural progesterone. By their reasoning, if testosterone has a "progestational" effect on the uterus (as it does), then progesterone will produce whiskers and big muscles. If no one had tried to point out to them the egregiousness of their errors, I could believe that the FDA was innocently incompetent, but in fact they actively work to obscure the truth.

In this case, and in others that I have discussed elsewhere, I believe the FDA has taken irrational and antiscientific positions to protect the interests of the giant drug companies, to the great detriment of public health. They, and the companies they serve, should be held accountable for the death and disability resulting from their actions. Legally, I think patients, physicians, and pharmacists all have many bases on which to act against the abuse of power by people in the FDA. Illogical and arbitrary application of the law is simply illegal.

Origins of Progesterone Therapy

Townsend Letter for Doctors, November, 1992

By the beginning of the 20th century, the idea of extracting regulatory substances from animal tissues was coming into general acceptance in Western medicine. J. A. Lebreton, in Paris, was one of the first to argue for the therapeutic use of an extract of the corpus luteum. Around 1904, C. F. Burnam, of Baltimore, began using corpus luteum of the sow, administered orally, to treat the nervous symptoms associated with menopause or with the menstrual cycle, and also to treat functional amenorrhea, obesity, sterility, and habitual miscarriage.[1,2] By the 1920s, tablets of desiccated corpus luteum were generally available, and the daily dosage recommended (representing 6 g to 18 g of fresh tissue) contained a very substantial quantity of progesterone.

The chemical structure of pure crystalline progesterone was determined in 1934 (by Butenandt), and within two years many publications were reporting the beneficial effects of injections of the purified material. By 1935, animal research was confirming that the therapeutic work previously done with the crude extract had been on the right track. Although the early research showed that progesterone was very beneficial in threatened miscarriage, arthritis, infertility, cancer, and functional diseases of the nervous system, interest in this generic, public-domain material faded as the pharmaceutical industry found methods for converting it into proprietary synthetic glucocorticoids, estrogens, and progestins.

Animals are generally more sensitive to progesterone than humans are, and in animals no toxic level has been found, except that in the highest doses it is anesthetic. In humans, even this effect has never been reported in the medical literature, and it is clearly anti-toxic in nature. Besides preventing acute poisoning of many kinds, it also reduces the incidence of birth defects and cancer.

Progesterone, The Protective Substance of Youth

In 1971, I discovered that vitamin E and progesterone work together to sustain efficient production and use of biological energy.[3]

In the mid-1970s, I found that progesterone is the most powerful order-preserving substance (anti-chaotropic) on the cellular level, and that this explains its range of protective actions, from anti-toxic to anti-stress.[4,5]

Around 1980, I discovered that vitamin E, with its crucial effect on the mitochondrial respiratory enzymes, is a uniquely powerful, stable, and biologically compatible solvent for progesterone.[6]

Their intimate association at certain cellular sites requires mutual solubility. This property of mutual affinity extends to all biological areas, meaning that the solution of progesterone in vitamin E can be administered with exceptional efficiency by application to the skin or other membranes, or by ingestion, where normal digestive processes convert it into chylomicrons and distribute it to all tissues, allowing it to escape the tendency of the liver to convert it rapidly to an excretory form, as occurs when progesterone is administered in other forms.[3]

Because of its profound biological compatibility, the progesterone-vitamin E solution permits otherwise impossibly high doses to be given, increasing by as much as 2000 % progesterone's already dramatic effects in a wide range of major biological problems, including epilepsy, habitual miscarriages, auto-immune diseases, and cancer of the uterus, breast, and kidney.

Some Aspects of Basic Progesterone Research

By 1945, Hans Selye had demonstrated that progesterone in itself has the full spectrum of regulatory and anti-stress functions of the adrenal steroids.

A little later, Albert Szent-Györgyi showed that progesterone is able to regulate the heart, in a manner similar to digitalis. In the 1970s, I demonstrated that it acts similarly on vascular smooth muscle, regulating its tone and preventing venous pooling of blood, and maintaining normal filling of the heart, opposing shock. The immediate improvement in circulation can have dramatic effects, which include restoration of kidney function, elimination of fluid from the lungs, restoration of sensation in the feet, and healing of gangrenous toes.

It restores normal tone to other smooth muscles, including the gall bladder, urinary bladder, intestine, sphincters, and uterus.

Progesterone's ability to regulate thresholds of cellular excitation operates in nerves, as well as in smooth and cardiac muscle. It sensitizes nerves that regulate respiration, and has been used to treat infant apnea, sleep apnea in adults, and polycythemia vera in men.

In cases of specific progesterone deficiency in men, small doses can cure impotence. It has been used effectively to treat benign prostatic enlargement.

It normalizes fluid pressure, as in bursitis and glaucoma treatment.

It restores many of the functions of aged skin, and is the normal defense against calcium loss from bones.

It is one of the few essential requirements, besides nutrients, for nerve (brain) cell growth and survival. In young people of both sexes, the brain contains more progesterone than other organs do.

It is reasonable that progesterone, the dominant hormone in pregnancy, should have a full range of protective functions to protect the vulnerable organism during its intra-uterine life.

Practical Issues

A typical dose of progesterone/vitamin E, 20 mg/day for 10 consecutive days, costs about $1.00 per month, at the present retail price.

Pharmacists have the authority to compound drugs as they choose, just as physicians can prescribe the formulation they prefer.

Neither progesterone nor vitamin E has any toxicity when used orally.

Under federal law, a prescription is needed for a dosage form of a drug that is potentially harmful. In practice, the very dangerous injectable insulin is always sold without need for a prescription, presumably because its use is conceived as akin to nutrition, providing an essential natural substance to restore a natural function of the body. By analogy with insulin, the infinitely less dangerous progesterone should not require a prescription.

The logical way to make progesterone/vitamin E available to the public would be to license the patent to a chain of drugstores.

The availability of this effective and economical form of progesterone can hardly be kept secret, because people tell their friends, and patients eventually convince their physicians that it works.

An exclusive licensing agreement would be possible with 10 % royalties, based on the retail price, with a guaranteed sales volume, and with lower royalties for larger volumes.

Economic Questions

Because of its absorption by a natural digestive route which distributes it to all of the tissues, progesterone dissolved in vitamin E is almost 100 % absorbed when taken orally. Less than 1 % is absorbed from some types of suppositories, and less than 5 % absorption is typical. Taken orally as a micronized powder, pharmaceutical efficiency is only slightly better.

Most of the valid human research before 1981 used intramuscular injections of progesterone dissolved in vegetable oil and benzyl alcohol. Benzyl alcohol has a high affinity for water, and in contact with the tissue fluid, it leaves the mixture, causing progesterone crystals to form, since vegetable oil is a poor solvent for progesterone. Therapeutic blood levels of progesterone can be achieved by intramuscular injections, but at the cost of leaving toxic debris at the site of injection. Benzyl alcohol is a powerful neuro-toxin, but its harm is reduced by progesterone's anti-toxic action. The cost of the injectable progesterone, and of the injection itself, has been the main factor preventing wider acceptance of this form of progesterone in the United States.

Natural progesterone, and closely related steroids, occur in a wide variety of organisms. Up to the present, the cheapest source of the raw material has been the wild *Dioscorea* yam of tropical Mexico, but soybeans have also been used as the source of a steroid for production of progesterone. Since the soybean is a major source of vitamin E, the finished product can be made anywhere the bean is produced. Fenugreek, a quick-growing plant, contains the same substance as the Mexican yam, and can also be used as a source of vitamin E.

The chemistry for converting crude diosgenin into pregnenolone, and for converting pregnenolone into progesterone, is very simple, and can be done with little capital, at the site of production of the raw material. Interstate commerce needn't be involved, except for the economy of scale.

Osteoporosis and the Skin

Townsend Letter for Doctors, April, 1996

WHILE I was working on my dissertation, around 1970, the opposition between stress-injury and energetic resistance became increasingly apparent to me. Estrogen (like X-irradiation, aging, or trauma) called up the cortisone response, and other factors, especially progesterone and thyroid, allowed the organism to restore itself in ways that neutralized the cortisone response.

Therefore, when I saw that the estrogen-like processes became more and more dominant after middle-age, it was natural to think of progesterone and thyroid as the main factors that should be replaced. This is why in 1975 I described menopause as resembling Cushing's syndrome, which is caused by a toxic excess of cortisol.

Osteoporosis, hot flashes, insomnia, and mood disorders are caused by cortisol, and so I tried using progesterone and thyroid—the anti-cortisol factors—for those conditions. The results were so profound that I began to study the general implications for health, and to try to understand the mechanisms so that prevention might replace treatment.

Several people who had been abandoned as hopeless terminal cases—with "epileptic brain damage," inflammatory degeneration of hip and thigh bones, diabetic gangrene, senility—recovered their health within a few days, and went on with their lives in productive and pleasant ways.

I knew that intense and frequent epileptic seizures cause the exhaustion and death of brain cells. A 52 year-old woman had been having seizures for over 15 years. Her neurologist gave her a mental exam every year, and considered her to be hopelessly demented. After using progesterone for a few days, she functioned normally. After about a year, she returned to graduate school at the University of Oregon, and got a master's degree with straight A's.

A 79 year-old woman had had artificial hip joints implanted when she was in her fifties, but her bones had weakened to the point that no further surgical repair was possible. She settled her affairs, and didn't expect to get out of bed again. After using progesterone topically and orally, after two weeks she was able to get out of bed and return to her normal activities. At the age of 85, she went camping on the beach in Mexico, and travelled to Scotland.

An 82-year old man was agitated and confused, and was apparently suffering from senile dementia. After being given progesterone and pregnenolone for a few days, his mind became clear, and he returned to work on scientific projects he had begun decades earlier. A squamous cell cancer on his lip regressed, and never bothered him again.

A 60 year-old woman had "osteoporosis" (shrinking) of the jaw bone that was causing her teeth to loosen. After applying progesterone solution to her gums daily for a few months, her teeth became firm.

When bones had almost disappeared from X-rays, yet became firm and functional within a few weeks, it was obvious that regeneration had taken place. But when brains went in a very short time, from imbecility or idiocy to intellectual productivity, I could only guess what might be happening to the cells. But I got a useful perspective on the mechanism of progesterone's action by seeing some recoveries that were even faster than those I have mentioned.

In animal experiments, I knew that estrogen causes cells to take up water within a few minutes after it reaches the tissue, and that this is at least partly the result of its interfering with the availability of oxygen. Within 40 minutes of administering a large dose of estrogen, the lungs become extremely inefficient at oxygenating the blood. This involves a sudden thickening of the alveolar membranes and the walls of capillaries, simply by taking up water. So, when I saw bulging veins disappear a few minutes after women took progesterone, along with a sudden lifting of extreme depression, I guessed that their circulation had become more efficient, and that better oxygenation had changed their mood.

Then, I repeatedly saw physical changes in other people that were visible within an hour, and that involved a sudden movement of water out of edematous tissues. In many people with damaged joint cartilage (confirmed by various types of examination, including arthroscopy), the joints became mobile in an hour, and by the next day, the defect no longer existed. A man who was purple from emphysema changed color within a few hours, and within a few days was going to work. The bulging eyes of exophthalmic Graves' disease receded into their sockets noticeably within an hour, and were normal the next day. Simply increasing the circulation couldn't have done those things. Opposing estrogen's edema-promoting action was involved, but I couldn't imagine any mechanism that could explain such rapid movement of water from the swollen tissue into the bloodstream.

One of estrogen's effects is to lower the amount of albumin in the blood. Estrogen causes the liver to synthesize less albumin, partly by causing the messenger RNA to be destabilized and degraded. (Iron can have some similar effects on liver RNA.) When there isn't enough albumin in the blood, water moves from the blood into the tissues, causing edema. (Premenstrually, edema might seem to be just a nuisance, but it can eventually become a serious problem, with aging or pregnancy, for example.) Albumin binds oily substances, and its conformation seems to be opened when it binds them. Progesterone is known to adsorb strongly to proteins—it has been called a "cardinal adsorbant," meaning that it can bind in ways that cause the protein's adsorptive capacity to change. I believe that progesterone and pregnenolone oppose estrogen in many ways, but the amazing speed with which they can cause major structural changes in the soft tissues convinces me that one of their first sites of action is the albumin molecule, causing its conformation to open in such a way that it is able to more strongly bind water molecules. This physical change in albumin would change the blood's osmotic/oncotic pressure, causing water to flow into capillaries. As the edema is reduced, oxygenation is more efficient, because the pathway for oxygen diffusion becomes shorter.

Albumin has been described as a first line of defense against toxins, since it binds them until the liver is able to degrade them chemically. Progesterone, pregnenolone, and cholesterol are known to increase the organism's resistance to a great variety of toxins. (Selye coined the name "catatoxic steroids" to describe steroids of this type.) If these steroids bind to albumin in a way that opens the protein to increase its binding capacity, that single process could explain the "catatoxic" effect, as well as the anti-edema effect.

When the blood is unable to retain its normal amount of water because of insufficient albumin/sodium, the blood volume is reduced as the tissues become water-logged. This causes the hematocrit (the proportion of cells in a volume of blood) to rise, and this increased packing of red blood cells causes the blood to become more viscous. Knisely studied this phenomenon in a great variety of sicknesses. Increased viscosity and slower flow decrease the blood's ability to deliver oxygen and nutrients to the tissues, including the blood vessel walls, modifying their tone. Slower flow, even without any changes in the fibrin/fibrinogen system itself, increases the formation of clots.

This description of progesterone's immediate action is intended to take some of the mystery out of its dramatic effects, but it isn't intended to argue against any of its actions within cells. It serves to give a general picture of how progesterone can systematically reduce stress and its harmful consequences, just by making blood circulation more efficient.

At first I most often used progesterone dissolved in olive oil to stop the stress-induced processes of deterioration, with a high protein diet to support the processes of repair. Now, I have added a variety of other techniques.

There always seems to be a rough balance between tissue regeneration and tissue degeneration, with growth and repair occurring when the equilibrium shifts in one direction, and with atrophy or degeneration occurring when the balance shifts in the other direction. If we can understand the mechanisms of atrophy, and how to retard or to block tissue destruction, then we can restore the balance to a degree which might allow regeneration to occur, even if we don't clearly understand the mechanisms of growth.

Skin and bones are such different types of tissue that it will be useful to start with them, because if we can see similar processes of degeneration or regeneration in them, then the chances are good that the same processes will occur in other tissues too. Bone is a relatively stable tissue, while skin is a tissue whose cells divide rapidly.

It is common medical knowledge that cortisone and related glucocorticoid-type hormones cause skin to atrophy, becoming thinner. Using topical applications of a synthetic derivative of cortisone, C. M. Papa and A. M. Kligman showed that the atrophy extended to the pigment cells, reducing their size and eliminating most of their dendritic branches. They also found that estrogen caused the skin to become thinner. The other steroids they tested, progesterone, testosterone, and pregnenolone, acted in the opposite direction, making aged and atrophied skin thicker and more regular. They also made the pigment cells larger, and increased their branching.[1]

Since these hormones were already known to have protective actions against cortisone and estrogen, these results were not too surprising, though they did directly contradict the claims of people who made estrogen-containing cosmetics.

Since progesterone and pregnenolone do not cause healthy, young skin to thicken, their effect in damaged skin is probably partly to replace

the deficiency of that type of steroid which occurs with aging, and to offset the damaging effects of the catabolic hormones, whose influence does not decrease with age.[2]

Many years ago it was found that in old age a woman's estrogens were increased relative to the 17-keto steroids adrenal androgens. Later, it was found that the conversion of androgen to estrogen increases with age in both men and women, and that this occurs largely in fat cells. Several years ago, P. K. Siiteri found that low thyroid modified the enzymes of fat cells in a way that would tend to increase the conversion of androgen to estrogen. More recently, it was found that adding progesterone to the enzymes had the opposite effect of aging and hypothyroidism, protecting the androgen from conversion to estrogen. These researchers (C. J. Newton and colleagues, of London) concluded that the decreased output of progesterone after the menopause might account for the increased production of estrogen.[3] Since progesterone declines in aging men, too, this could account for the same process in men.[2]

Vitamin A's effect on the skin opposes that of estrogen. There are several mechanisms that could account for this.[4] Vitamin A is used in the formation of steroids, and since the skin is a major site of steroid metabolism, vitamin A might help to maintain the level of the anti-catabolic steroids. A deficiency of vitamin A causes excessive release of the lysosomal enzymes, acid hydrolases, resulting in tissue catabolism.[5] Also, vitamin A is necessary for the proper differentiation of cells in skin and other membranes. A deficiency tends to cause an increased rate of cell division, with the production of abnormal cells, and a substitution of keratinized cells for other types. Estrogen also promotes keratinization and speeds cell division. A deficiency of vitamin A can cause leukoplakia in the mouth and on the cervix of the uterus; although this is considered "pre-cancerous," I have found it to be very easily reversible, as I have discussed elsewhere.[6] I suspect that the intracellular fiber, keratin, is produced when a cell can't afford to do anything more complex. Adequate vitamin A speeds protein synthesis,[7] and allows it to be used more efficiently.

Prolactin (which is promoted by estrogen, and inhibited by progesterone) increases with stress and with age. It probably affects every tissue, but it seems to have its greatest effects on the secretory membranes. It is known to have strong effects on the kidney, gut and skin (sweat and oil glands, hair follicles, and feathers in birds), and on the gills of fish.

Its involvement with milk production suggests that it might mobilize calcium from bones, and in fact it does contribute to osteoporosis. This was foreseen by G. Bourne, in his book on the metabolism of hard tissues, when he suggested that estrogen, acting through the pituitary, might be expected to promote osteoporosis.

Since reading Bourne's book, I have doubted that it was rational to use estrogen to prevent osteoporosis, especially when it is known to be carcinogenic and when the ratio of estrogen to androgens and progesterone increases after menopause. Now that several publications have appeared clearly showing that estrogen increases prolactin, that prolactin increases with aging, and that prolactin contributes to osteoporosis, the postmenopausal use of estrogen is worse than dubious. But this was exactly when the pharmaceutical companies needed help in continuing to sell their profitable estrogens, and this was exactly the time when the FDA came out with its official approval of estrogen for preventing osteoporosis.[8]

Some doctors combine estrogen with testosterone, and this is much safer and more likely to keep the bones healthy. But since testosterone, like estrogen and cortisone, causes the thymus gland to atrophy, it is not a very good idea for chronic use, even if it doesn't cause masculinization. The other anti-estrogens, which are present at high levels in young women, include progesterone and DHEA. I have seen several publications which I think would justify the use of physiological amounts of DHEA to prevent or to treat osteoporosis,[9,10] and a few which support the use of progesterone.[11,12] My own observations on their use in osteoporosis have been presented many times at alternative medical conferences since the 1970s, but the main-line medical journals and conferences have declined to accept my reports, even when they advertise that all papers submitted will be presented in some form; many physicians believe that they are being presented with a fair sampling of the work being done in endocrinology, when in fact they are being given intensive advertising sessions.

Since it is known that cortisol causes bone loss, and it is widely accepted that progesterone has an "anti-glucocorticoid" action, it is reasonable to think that progesterone should protect against bone loss, and that it is a progesterone deficiency after menopause which is a major factor in the development of osteoporosis. In the first edition of *Nutrition for Women* (1975) I pointed this out, in comparing menopause to Cushing's

disease. Nencioni and Polvani more recently made observations which support this mechanism, in which progesterone "exerts a protective effect," by blocking the corticosteroid receptors. They observed "that the process of rapid bone resorption starts before the onset of amenorrhea and the abrupt fall in the estrogen levels and coincides with decline in progesterone secretion."

By improving blood circulation and oxygenation of the tissues, progesterone and pregnenolone will decrease the need for the body to produce cortisol. Pregnenolone acts in the brain to decrease the basal secretion of ACTH. This protective effect is more basic than that achieved by blocking the cortisol receptors.

The early tests of the toxicity of vitamin A used cartilage in tissue culture. The same enzymes which are released by a deficiency of vitamin A are released by a large excess, causing dissolution of the cartilage. Other studies showed that a vitamin A deficiency caused similar changes in both bone and cartilage. Although much vitamin A is consumed in the production of progesterone, these studies show a direct effect of the vitamin on tissue stability. Although I believe that a vitamin A supplement will offer considerable protection against osteoporosis (and also against aging of the skin), it is important to remember that excessive vitamin A inhibits the thyroid, and that there is less risk of toxicity when vitamin E is supplemented too. I think many of the headaches currently associated with vitamin A use are the result of a preservative in the capsules (probably a sulfite), since some people who react to the vitamin in capsule form don't react when they use a specially ordered bulk form prepared without preservatives.

Things which damage skin and bones also damage other tissues, and things which protect them also protect other tissues. The protective factors include hormones (thyroid, DHEA, progesterone, and pregnenolone), vitamins A and E, and minerals—including magnesium, calcium, and sodium. Sodium spares magnesium, and helps to make albumin function in regulating blood and tissue water content. Under some conditions, sodium can act as an antioxidant. Since the unsaturated oils (and their prostaglandin derivatives) decrease respiration, cause stress to be more harmful, and have some specific effects that promote aging of skin, bones, and other tissues, the use of coconut oil is especially important. I think its use is one of the factors that prevents osteoporosis in tropical countries.

Progesterone Can Be Taken Orally

Townsend Letter for Doctors, November, 1994

YOUR June review of Betty Kamen's book on hormone replacement in menopause, osteoporosis, and PMS made some good points, but it repeats a serious error, that progesterone "cannot be taken orally."

I believe that idea was a simple fabrication of someone in the drug industry in the 1940s to promote their own new synthetic progestin, because I could never find the source for the idea, which simply began appearing in the literature without supporting data, when new products needed promotion.

Human milk from healthy women contains significant amounts of progesterone, which makes milk an important part of the infant's endocrine system. Associated with fat droplets, progesterone enters the blood by the chylomicron pathway, permitting it to avoid inactivation or excretion.

When taken in the powdered or micropulverized form (even if the powder is packed in oil) progesterone doesn't enter the blood as chylomicrons, and so is quickly processed into a water-soluble metabolite, which is excreted. This metabolite cross-reacts with active progesterone in the usual analysis of blood levels, and creates some medical confusion, since symptoms and measurements don't relate in the usual ways.

Betty Kamen cites my book, *Nutrition for Women*, as a source for the idea about oral progesterone. I believe she might not have read my material itself, since my comparisons in that book had to do with the superiority of skin-absorption over injected progesterone. In many other publications, including *Progesterone in Orthomolecular Medicine* (all my books are available directly from me), and several articles in the *Townsend Letter*, I have described the efficacy of oral progesterone dissolved in vitamin E.

I have the patent on that form, and some manufacturers have unscrupulously implied that they are using my formula. I have tested several such preparations, in preparing my patent infringement case. Recently I have examined some of the products of a Portland company (a company which has led many people to think I am involved in their business). What I found was that the progesterone had rapidly gone out of solution, forming bizarre hair-like crystals, which gave the solution

a slightly stringy texture. Natural progesterone in natural vitamin E remains stable in solution, and I believe the only explanation for the bizarre crystallization that I and others have observed would be the use of synthetic polymer-substances in the solution. In that form, it doesn't infringe my patent, but it would seem to be mislabeled and misrepresented.

The FDA has erroneously classified progesterone with synthetic progestins, and hasn't made any attempt to help the public separate promotional fictions from physiological facts. In fact, they have themselves created additional fictions about progesterone, ascribing properties of the synthetic progestins to progesterone itself, resulting in tremendous injury to the public health. (If that agency strictly followed the rules of administrative law, it might not be perceived as the servant of the industry which it is supposed to regulate.) The ineffectiveness of oral progesterone is one of the fictions that needs to be corrected, and the popular and alternative medical press is where that correction can be achieved. Betty Kamen's book is better than most of the books on osteoporosis and menopause, but it looks a little too much like a promotional effort in support of Dr. Lee's cream, and I am sorry that one of my books is mentioned as seeming to support the fiction that the skin cream is better than the oral oil form.

If she ever rewrites the book, I hope she will consider the evidence that thyroid hormone plays a major role in rebuilding bones, and that unsaturated oils (via prostaglandins and a variety of other hormonal derangements) and estrogen (via promotion of prolactin) have a role in causing osteoporosis. Oral progesterone dissolved in vitamin E is a powerful protectant of every system and tissue, including the bones, but it is important to understand its wonderful effects in the contexts of physiology and ecology. I think the properties of natural progesterone provides us with a scientific paradigm, similar to the concept of "adaptogens" in medicine, but even more basic, involving physical self-ordering processes. Increasingly, our health will depend on understanding this paradigm of life's resistance to harm.

Progesterone Content Corrected

Townsend Letter for Doctors, June, 2000

BURTON Goldberg's article on fibroids[1] indicates that Aeron LifeCycles lab reported the progesterone content of Progest-E Complex as being between 1000 mg to 1500 mg per ounce. I was told a couple of years ago that this figure was mistakenly introduced into John Lee's book by the book's editors. That product, made under my patent, has never deviated from its 10 % progesterone content, so it contains 2850 mg of progesterone per ounce, and I don't know of any test that has found otherwise. As I understand it, Dr. Lee's book was later corrected.

Progesterone: Essential to Your Well-Being

Tides of Life, January, 2000

THE hormone progesterone participates in practically every physiological process, in both men and women. Its tremendous increase during pregnancy serves to stabilize the organisms, both mother and child, during that crucial time. At levels reached just before delivery, progesterone produces anesthesia and contributes to tissue elasticity. The fetus requires large amounts of glucose, and progesterone makes it possible to be provided in abundance for ideal brain growth, by promoting the mother's ability to use fat for her own energy. It is this efficient use of fat which gives women greater long-range endurance than men. When progesterone is deficient, there tends to be hypoglycemia, often combined with obesity.

The stabilizing action of progesterone is especially visible in muscle tissue, such as the uterus, blood vessel walls, the heart, the intestines and the bladder. Less visibly, progesterone stabilizes and normalizes nervous, secretory and growth processes. Biochemically, it provides the material out of which all the other steroid hormones (such as cortisone, testosterone, estrogen and salt-regulating aldosterone) can be made as needed. Progesterone's simple molecular structure allows it to balance either an excess or deficiency of those other hormones, even when there is a defect in their synthesis.

Many factors, including poor nutrition, climate, emotional or physical stress (even excessive running) and toxins, can cause a progesterone deficiency. Use of estrogens, birth control pills and even IUDs can also bring about a deficiency. Animal studies and clinical experience suggests that the prenatal hormonal environment (a mother's excess of estrogen during pregnancy) can incline a person toward a deficiency of progesterone relative to estrogen.

Recent studies show that progesterone prevents stress-induced coronary blood vessel spasms in aged hearts-probably explaining women's relative freedom from heart attacks, so long as they retain functioning ovaries. Other studies suggest that progesterone has a role in regeneration of damaged brain cells and prolonged growth of the brain. Delayed aging and longer life span have been very clearly related to extra progesterone. Many types of tumors have been prevented and helped

with progesterone. Excessive blood cloning caused by excess estrogen alleviated by progesterone. Pregnancy toxemia and tendency to miscarry or to deliver prematurely are often corrected by progesterone. When epilepsy occurs premenstrually, or first appears around puberty, it is often stopped by progesterone therapy. The hormone has been used successfully in suicidal depression, Reynaud phenomenon, Meniere's disease, agoraphobia (especially when associated with porphyria, an abnormality of liver metabolism), Bright's disease (a kidney disorder) and, used as a lotion, in a variety of genital skin problems in children, adults and postmenopausal women. Hot flashes and other menopause problems respond to progesterone therapy.

Since progesterone normalizes the immune system (it causes thymus regeneration, for example) it is very effective in autoimmune diseases (which result from adverse reactions to one 5 own tissues) and in those degenerative disease which have an autoimmune component.

In several ways both progesterone and thyroid hormone can be considered primary regulatory hormones. Both of them regulate metabolism directly at the energetic and synthetic levels: both have a normalizing, anti-stress action on the pituitary gland; and each has a promoting action on the other. Both are blocked (and consumed) by stress and promoted by light and good nutrition. Both are nutrients in cultures that eat the whole animal, including ovaries and thyroid, butter, cream and milk contain small amounts of progesterone and shellfish seems to be a good source.

Disregarding most of the information promoted by pharmaceutical companies and the medical texts and journals which for 30 years have reflected the opinion of those companies (especially regarding the patented synthetic estrogens and glucocorticoids), we can trace a line of research and ideas on the sex hormones, from pioneers such as Loeb, Korenchevsky, and Selye, through a generation that continued to demonstrate the toxicity of estrogen, and the value of progesterone including people like Lipschutz, Dalton and Soderwall.

In my dissertation research under Soderwall, I had the opportunity to collect and assimilate data indicating an increased estrogen effect in aging animals and recently, with newer techniques, I have seen similar changes in many menopause women. My research showed that the probable mechanism by which estrogen excess causes infertility is through limiting the availability of oxygen. I showed that anti-estrogenic

substances, such as progesterone or vitamin B, increased the oxygen content of the uterus. This anti-oxygen effect of estrogen suggests a convergence of reproductive aging research with Warburg's theory that damaged respiration is the primary defect in cancer and also with Selye's observation that estrogen's effect resembles the first shock phase of stress reaction.

Early research had also shown that estrogen diminishes liver glycogen storage while progesterone increases both blood sugar and liver glycogen. It is well known that hypoxia (oxygen deficiency) damages the fetal brain, but probably less well known that hypoglycemia—either chronic or acute—can cause brain damage and retardation. Oxygen deficiency, by lower metabolic efficiency, will cause hypoglycemia. Estrogen causes hypoxia at every imaginable site, from lung, through vascular fibrin (clot material lining blood vessels and red cells) and extracellular collagen (a glue-like part of connective tissue) and edema, to intracellular metabolism. Estrogen is also a promoter of insulin release and action, lowering blood sugar and promoting fat synthesis. Estrogen and another common anti-oxygen material, excessive unsaturated fats (vegetable or fish oils) have both been demonstrated to cause the birth of small-brained, retarded animals. Recent studies imply that about half the children identified as hyperactive have experienced prenatal stress. The most urgent need for progesterone therapy, I think, is preventing a continuing epidemic of brain damage. Beyond that, many studies have found that the use of natural progesterone increases a child's IQ, typically by around 35 points and produces personalities that are more "independent, individualistic, self-assured, self-sufficient and sensitive."[1]

Progesterone vs. Hypoglycemia

Protection against hypoglycemia is probably the main mechanism. Diabetic mothers often have precocious children, if they aren't damaged by drugs and irrational diets. 10 g to 15 g per pregnancy, at increasing dosage, seems to be the optimal amount, when there is some sign of excessive estrogen or unexpected toxemia. The American Medical Association Department of Drugs, which warns against certain sex hormones being used during pregnancy, has specifically excluded progesterone from those others which are "now contraindicated in early pregnancy."[2]

Hypoglycemia (which can result from any respiratory defect) can produce malfunction of any tissue, but brain dysfunction and immune dysfunction are very common effects. Adamkiewics has shown that allergic reactions to a given substance will decrease from 100 % to 0 %, when the blood glucose increases from, for example, 50 mg to 150 mg or more. Soviet research shows a similar involvement of blood sugar level in various "psychosomatic" ailments. Progesterone (and thyroid) will help in most allergic diseases, including the autoimmune and "collagen diseases," because it helps to maintain blood sugar (promoting respiration and improving use of fat-sparing glucose) and also because it stabilizes lysosomes (enzyme packets in cells, which are involved in inflammation processes).

The group of enzymes known as superoxide dismutase (SOD) are probably involved in the protective effects of progesterone, since one of my assays to determine the action of estrogen turns out to be an inverse indicator of SOD-that is, progesterone would seem to turn on this protective enzyme.

Although progesterone and cortisone both raise blood sugar and stabilize lysosomes, their effect on the brain is very different. In large doses, progesterone is sedative and anesthetic, while cortisone is stimulating and causes changes in the brain, which resemble aging. An excess of cortisone also tends to elevate estrogen, which was found (in animal experiments) to interfere with memory. High estrogen traits can be acquired by environmental stress and can be passed on to offspring, as discovered by L.C. Strong in his mice, and as confirmed recently in rats that were stressed during pregnancy.

It has been observed that the ratio of brain weight to body weight corresponds directly to longevity. The brain has a nourishing, trophic influence on other tissues. A stable, efficient brain is an anti-stress agent. The hormones of stress age various tissues, including connective tissue. Good nutrition, including the anti-stress substances found in certain foods, will simultaneously optimize intelligence and increase the healthy life span. Congenital defects are increased by stress and poor nutrition during pregnancy and, conversely, reduced by good nutrition hormone supplementation and stress reduction.

An excessive estrogen/progesterone ratio is more generally involved than either a simple excess of estrogen or a deficiency of progesterone, but even this ratio is conditioned by other factors, including age, diet,

other steroids, thyroid and other hormones. The relative estrogen excess seems to act by producing tissue hypoxia. Symptoms in cycling women are most common around ovulation and in the premenstrual week, when the estrogen/progesterone ratio is normally highest. The early 20's, late 30's and menopause are the periods when the ratio is most often disturbed. These are also the ages when thyroid disorders are commonest in women.

I have observed the use of progesterone transdermally (applied to the skin) in about 400 women suffering from the full range of perimenstrual symptoms, including migraine, acne, depression, mastalgia (breast pain), edema (water retention and swelling), and lethargy. I found that nearly all the women who apply the lotion themselves, are able to find the appropriate dosage for controlling their symptoms. Occasionally, thyroid therapy, weight reduction: or change in some aspect of lifestyle is necessary for complete relief from symptoms. When some women said the progesterone had no effect, it turned out that they were applying it as sparingly as they would a rare perfume-just touching it to their wrists.

Anesthesia (or drunkenness) from a very large overdose is the only negative side effective reported in the literature. Experimenting with very large doses of natural progesterone on myself, for migraine, I found that there is a temporary antagonism to testosterone, causing small symptoms, including a slight sense of gregariousness, an urge to socialize. However, synthetic progestins do have harmful side effects including breast tumors. Unfortunately, most physicians do not yet know the difference between natural progesterone and synthetic progestins.

At our health resort/clinic, we're finding that most women respond dramatically to progesterone support, but don't remain chronically dependent on it. During their stay, clients are provided specialized, indulgent care, along with progesterone and other therapies. We consider it essential, as well, to teach them the principles of maintaining optimum health through good nutrition. Results are impressive and usually permanent.

Repairing Immunodeficiencies

Townsend Letter for Doctors, November, 1989

Last summer's death of most of Europe's seals from viral diseases suggests the possibility that their immune systems were weakened. The coincidental publication last spring of a study of the relatively remote Arctic seals of Spitzbergen,[1] which found surprisingly high levels of dioxins and other toxins in the animals, suggests that the aquatic carnivores closer to the sources of pollution might simply have been the first large group of animals to reach an intolerable level of chemical immunosuppression. The people who eat the same fish that the seals eat, and breathe the same air, might also be experiencing some degree of increased susceptibility to infections.

For several decades, the death rate from some kinds of opportunistic infection has been increasing,[2] and as bacterial infections came under control in the 1960's they tended to be replaced by less common infections such as *Pneumocystis carinii*.[3]

Acquired (or secondary) immune deficiency has been a familiar phrase in immunology for at least a generation, and the recognition of the condition itself, under different terms, has been part of medical knowledge for many generations. Before 1981, typical textbooks listed cancer, chemotherapy, ionizing radiation, malnutrition, aging, parasites, fungal infections, and viral infections among the known causes of acquired immune deficiency.[4]

After 1981, the term "acquired immune deficiency syndrome" was appropriated by the molecular virologists, who were familiar with the ability of viruses to cause immunosuppression, and who, with impressive speed, determined that the "new" syndrome was caused by a certain new virus, the human immunodeficiency virus (HIV) or the human T-cell lymphotropic virus type III (HTLV-III).

Peter Duesberg was one of the few molecular virologists who doubted that a virus of that sort, all by itself, could cause disease.[5] An important implication of the identification of the HIV as the cause of AIDS has been—for the molecular virologists who ignore Duesberg—that a specific vaccine or genotoxic chemical should be able to destroy the specific pathogen. Very little attention has been given to the question of whether a person's good health can be maintained despite the presence

of the "viral gene." And the lingering effects of the "central dogma" of molecular genetics still discourage serious investigation of the question of whether such genes can be cleared from the genome under certain conditions without destruction of the cell.

Since human exposure to known immunosuppressants has been increasing during the years that the incidence of opportunistic infections has been growing, a real investigation of the cause or causes of AIDS will involve doing some scientific epidemiology, to learn whether some factor other than the HIV has a crucial role.

Some of the factors that I have given attention to, in working with "ordinary" (i.e., complex, traditional) immunodeficiency—*viz.*, a deficiency of the anti-glucocorticoid hormones, a dietary excess of iron and unsaturated fats,[6] a nutritional deficiency of vitamin A, folic acid, copper, and protein, an exposure to pediculocides and other chlorinated hydrocarbons including dioxins, etc.—should probably be included in such an epidemiological study. Even if such factors turn out not to be crucial in AIDS-HIV, my informal studies and observations since 1973 indicate that examining and correcting as many of them as possible can, inexpensively and safely, promote recovery from many chronic infections and other diseases associated with some degree of acquired immunodeficiency. Whatever the cause of AIDS associated with viral infection may be, it is likely that an appropriately designed supportive treatment will at least slow the progress of the disease.

In spite of a few virologists who still claim that there is no such thing as an immune stimulant, hundreds of immune-promoting substances have been studied and described, and a few of them (e.g., levamisole, inosiplex) are well-known. Although more meaningful tests are now available, skin tests have been used for several decades to demonstrate that immune stimulants or improved nutrition[7] can reliably shift the immune system from anergy to reactivity. Anything that intensifies metabolism tends to be an immune stimulant, other things being equal. A subnormal temperature is a common feature of chronic infection and early cancer, until a late stage of intense catabolism with fever.

Since most of the immune stimulants are harmless, compared to the genotoxins, the reluctance to test them is ideological, rather than scientific. My *Stedman's Medical Dictionary* (23rd edition) illustrates the psycho-linguistic environment: "immunodeficiency" and "immunodepressant" and "immunosuppressant" are defined in a way that any

native English speaker would understand. However, "immunological enhancement" (p. 464) is explained as involving the suppression of cell-mediated immunity (to prevent rejection of a tissue allograft). A major part of the history of medicine seems to have dropped out of medical English.

In one line of thinking a variety of malfunctions of immunity can be created by a single factor, such as energy deficiency, acting within the organism's special history or constitutional individuality. Allergies, auto-immune disorders, and chronic infections or skin-test anergy, can be seen as aspects or phases of a generally impaired reactivity of the organism, shaped by many trophic influences of nerves, hormones, nutrition, and by toxins, temperature, radiation, etc.[8] Accordingly, I have recommended the use of techniques of immunity-promotion (or normalization) for allergies, auto-immune disorders, and chronic infections or immune deficiencies, taking into account the person's history of environmental insults, nutritional deficiency, family traits, and present hormonal, nervous, and metabolic status as far as possible.

Beginning in 1973, a clinic in Eugene, Oregon (a city which is notorious for allergies, because of the surrounding grass-seed farms which produce pollen in the spring, and smoke from field-burning in the summer and fall) had very good results with their allergy patients when they gave them supplements of vitamin A, pantothenic acid, and vitamin C. Later, thyroid extract or triiodothyronine and magnesium were added to the other supplements for patients who had problems more serious than ordinary allergies. We found that many people with acne, bladder or kidney infections, periodontitis and sinusitis seemed to be deficient in both thyroid and vitamin A even when they were taking supplements of those materials. At higher doses of both, many of those people quickly got over their infections. Many people with colitis, myositis, bursitis and arthritis had sudden relief from their symptoms on this, or a similar program. We have assumed that some toxin might be interfering with the biological effects of thyroid and vitamin A.

If thyroid and vitamin A can't be used efficiently to form steroids, a steroid imbalance is likely. Unopposed cortisol is immunosuppressive in several ways, including thymic hypoplasia,[9,10] depression of the histaminolytic activity and mono-oxygenase activity of the liver, contributing to chronic allergies,[11] and it can induce the expression of some types of retrovirus.[12]

Although one of the important functions of vitamin A is its involvement in the formation of the steroids pregnenolone and progesterone (both of which moderate the effects of cortisol), it also has some hormone-like actions directly on the cells of the immune system, and it stimulates production of interleukin-2 and both inhibits generation of specific suppressor cells and limits the intensity of activation of suppressor cells.[13] The possibility of vitamin A toxicity is reduced by using the thyroid hormones and vitamin E.

Pregnenolone and progesterone have a vitamin A-sparing effect, besides their direct protective action for the thymus, and they also have the very general protective action which Selye called "catatoxic." Both of these hormones have been effectively used to treat various auto-immune ailments. They tend to raise the body temperature and metabolic rate, yet they are anti-catabolic.

Vitamin A, thyroid, progesterone, and the related steroid, dehydroepiandrosterone, all oppose estrogen, which has several immunosuppressive effects, including a cortisol-like thymic atrophy, hypoactivity of T cells, and reduced production of gamma-interferon and interleukin-2, reduced natural killer cell activity, and it probably has a role in the development of some auto-immune diseases.[14] Subnormal body temperature promotes estrogen secretion.

AIDS, which has been called "slim disease" in Africa, often ends with extreme wasting. Many physicians are horrified at the thought of treating immunodeficiency with thyroid, because they associate hyperthyroidism with weight loss. Two young women, who were diagnosed as having "allergies" and supposedly auto-immune pituitary hormone deficiency, and who each weighed around 70 pounds and was considered to be "terminal" (though they both ate normal amounts of food), recovered quickly with a thyroid supplement and a diet emphasizing eggs and fruit. About 80 years ago, when surgery was first being done to remove goiters, the whole gland was removed, no supplementary thyroid hormone was given, and the patients often died of a wasting syndrome, which was named "cachexia strumipriva." Thyroid function is essential to all cell processes, including protein assimilation and synthesis, formation of growth hormone, etc. Without thyroid hormone to sustain respiration, inefficient glycolysis wastes energy; unoxidized lactate provokes catabolism of liver protein. Hypoglycemia stimulates secretion of glucocorticoids, which maintain blood sugar at the expense of rapid catabolism of protein. It

is characteristic of people dying with AIDS to have no thymic tissue, as well as having other signs of extreme stress. It seems clear that a safe anti-stress, anti-cachexia, thymus-protecting program would have prolonged their life.

Triiodothyronine is often the essential factor in reversing a cachectic state. Although optimal thyroid function can increase the metabolic rate, it is not catabolic because it maximizes bioenergetic efficiency.

Adamkiewicz demonstrated the importance of blood glucose in anaphylaxis and allergy.[15] In a vicious circle, histamine tends to exacerbate hypoglycemia (e.g., by its acetylcholine-like actions) and it is directly immunosuppressive in many ways. It inhibits lymphocyte proliferation in response to stimulation, it inhibits antibody formation and lymphocytotoxicity, it suppresses cutaneous delayed hypersensitivity and release of lymphokines, and it suppresses both the generation of T-helper cells and their effector functions.[16–19] Besides the ordinary antihistamines and receptor blockers, the release of histamine can be inhibited by many other substances which are immunoprotective, such as epsilon-aminocaproic acid, and by the saturated fatty acids, from pentanoic to dodecanoic.[20] These fatty acids are known to be assimilated as quickly as glucose, and so it seems likely that part of their antihistamine effect is similar to the glucose effect demonstrated by Adamkiewicz, and that both effects could be largely the result of increased availability of metabolic energy. Since tumors often contain very large quantities of mast cells, immune therapy for tumors should take histamine into account. Since 1970 I have experimented with some unconventional anti-inflammatory substances, including some of the local anesthetics, which seem to have a safe and effective antihistamine action. I think some of the anti-cholinergics which have "anti-viral" activity (e.g., amantadine) are analogous in their mechanisms of activity.

Around 1960, ammonia was found to have an "anti-viral" effect, apparently by altering the host cell's structure or function, rather than by a direct virucidal action.[21] Following that discovery, many amines were found to have some anti-viral activity. Local anesthetics, anticholinergics, and the anti-viral amines can be thought of as a pharmacological family. Inosiplex apparently takes advantage of some of those properties, and it too acts on the cell, rather than on the virus.[22]

The central inhibitory system regulated by gamma-aminobutyric acid, the GABA-ergic system, is protective against stress,[23–25] and ap-

pears to protect immunity by limiting the organism's recourse to cortisol, and by supporting the synthesis of alternative steroids.[26,27] Gamma-hydroxybutyrate and its lactone are closely related to GABA metabolic pathways, and have anesthetic and anti-stress protective effects which appear to result mainly from central inhibition, and from an anti-glucocorticoid effect. The lactone has been found to have a strongly protective effect against intra-cerebrally inoculated viruses,[28] and it is remarkably non-toxic. The anesthetic and anti-convulsant effects of progesterone probably synergize with and reinforce the GABA-ergic system.

Many other substances of low toxicity have beneficial effects on the immune system or on some other aspect of resistance, and might be considered in an integrated approach to immune restoration.

Just as optimal nutrition must take age and other factors into account, an integrated therapy for immune deficiency must be sensitively designed for the needs of the individual. In many places where AIDS-HIV patients are treated, a panic mentality has taken over, and ordinary supportive therapies are neglected or rejected because they are outside of someone's "treatment protocol." A stereotyped protocol can be appropriate when therapy is directed toward the mechanistically understood elimination of a pathogen, but in therapy to strengthen immunity, individualization, alertness, and judgment are more appropriate. The complex nature of every patient should be recognized, in deciding what materials to use and how to use them.

Resistance of the Heart

Townsend Letter for Doctors, June, 1992

THE heart gives us some clues to our general resistance to stress, aging, disease, and death. The heart and the brain are the most stress-resistant organs, and while moderate stress and malnutrition can cause the skin and thymus gland to lose more than 90 % of their substance, only the most prolonged and intense stress can cause the heart and brain to lose more than a fourth of their substance. In fact, a moderate stress that causes the thymus to shrink by more than 90 % can cause the heart to increase its mass by 80 %. When we are able to respond adequately and adaptively to stress, there is a transfer of substance from the lower-functioning organs (usually the skin and thymus) to the organs that are bearing the greatest burden, usually the heart and the brain.

The glucocorticoid hormones of stress play the important catabolic role of mobilizing substances from the "idle" organs to support the working organs. The many ways in which the heart is able to resist stress, and even to thrive on it, can be generalized to develop ways to protect other organs, and the whole body, from the chronic and cumulative stresses that lead to generalized atrophy, declining function, and aging.

During stress, the heart and other working organs become resistant to the glucocorticoid hormones. When a person is given radioactive testosterone, it can be seen to reach the highest concentration in the heart. It is testosterone's anti-glucocorticoid effect which causes it to enlarge skeletal muscles, when exercise is moderate. Its parallel effects on skeletal muscle and heart muscle can be seen in highly adapted (stressed) long-distance runners, since the walls of their hearts become thinner as their skeletal muscles become slimmer. The other anti-catabolic steroids, pregnenolone, progesterone, and dehydroepiandrosterone (DHEA), are present in larger amounts, and are of more general importance, than testosterone, especially in the brain, where their concentration is very high. Albert Szent-Györgyi showed that the heart responds to progesterone, and more recently other researchers have presented evidence that DHEA is our "endogenous digitalis."

During moderate exercise, adrenalin causes increased blood flow to both the heart and the skeletal muscles, while decreasing the flow of blood to other organs. The increased circulation carries extra oxygen

and nutrients to the working organs, while the deprivation of oxygen and glucose pushes the other organs toward a catabolic balance. This simple circulatory pattern achieves to some extent the same kind of redistribution of resources, acutely, that is achieved in more prolonged stress by the actions of the glucocorticoids and their antagonists.

Stress—a need for adaptation—can be seen as an "information gap" between the need and the possibility of meeting the need. Appropriate modification of the organism's structure closes that information gap. The new "structural trace," or memory, can develop as either a phenotypic or genotypic change. "Mutations" are important for bacterial adaptation, and learning is important for mammalian adaptation.

Stress physiology is now recognized as a universal and basic part of life, for plants and micro-organisms, as well as for vertebrates. Our brains are the newest and most powerful organs of adaptation and resistance to stress, allowing the simpler systems of circulation and metabolism to orient themselves appropriately to achieve the most benefit with the least damage. Just as there are pro- and anti-catabolic hormones and circulatory patterns, the brain has stress-promoting and stress-limiting systems. When perception and orientation govern the stress reaction, the ability to suppress certain parts of the reaction permits fine coordination and high efficiency. Sleep is a generalized stress-limiting function of the brain. Another example of how the brain governs the energy-mobilizing system in stress was demonstrated by Seligman: Rats that experienced "capitulation stress," being held still until they quit struggling, drowned in a few minutes when they were put into a tank of water. But a single experience of successfully struggling to freedom caused rats to swim for many hours before becoming exhausted.

A single experience, an insight, has tremendous power to shape the way in which a rat deals with stress. Insights and ideas can be gained through practice, but they can also be passed on culturally. We can learn how to prepare ourselves to respond optimally to stress, while also trying to keep the environment from becoming too stressful.

Blue-collar workers have more heart attacks than do sedentary workers, and the "biosocial" stress of low status can be seen as a powerful factor in mortality from heart attacks. The helpless feeling of low status is analogous to capitulation stress. When stress is strong enough and long enough to overcome the multiple protective systems of the heart, the heart fails in certain well-defined ways, both functionally and

structurally. But before injury occurs, the stress-limiting "self-restraint" systems of the heart, of the endocrine system, and of the brain, will have to fail. Considering some problems of blood circulation will help to see the integral nature of adaptation, when it succeeds and when it fails.

Pregnant women sometimes develop very high blood pressure. In the 1950s, when new diuretics were being promoted by the drug companies, it became standard practice to give pregnant women diuretics and a low-salt diet to control their blood pressure. It should have been obvious (and it was obvious to people like Tom Brewer who thought physiologically, rather than mechanically) that the increase in pressure was the body's response to an increased need for circulation. As the fetus grows, the blood volume must expand, to meet the increased circulatory needs of the uterus, placenta, and fetus. Two research projects showed that very large supplements of salt reliably normalized the high blood pressure in women with "toxemia" of pregnancy. Other studies showed similar results with a supplement of progesterone. When the blood volume is able to expand as needed, circulation is adequate at normal pressure. When blood pressure is forced down by administering a diuretic to further diminish an already inadequate blood volume, the circulation of oxygen and nutrients to the fetus is seriously impaired, and a huge epidemic of mental retardation and hyperactivity, associated with low birthweight, began in the 1950s, and continued until eventually the fear of malpractice suits stopped the absurd practice.

A few years ago I asked a recently graduated physician what things he would want to consider in a patient with high blood pressure. Some of his suggestions for therapy were very reasonable, but his approach made it clear that he was thinking of circulation in a mechanical way, exactly as a skilled plumber would go about normalizing the circulation of water, without caring very much about what the water was being used for. The circulation of blood is nicely adjusted to meet the demands of the tissues. Blood pressure increases gradually with age, and individuals whose blood pressure stops increasing with age have been found to have a shorter life-expectancy than normal. Apparently, aged tissue is less efficient, and needs a more strongly pumped stream of blood.

When I found, around 1970, that the pressure of oxygen was low in old animals and in animals that had been treated with estrogen, I tried to determine the reason for the oxygen deficiency in each case. I found that in old individuals (hamsters or humans) the blood was only

about 50 % oxygenated as it passed through the lungs, as if diffusion into the capillaries was impaired. Estrogen treatment (rats and humans) does the same, apparently by causing a sort of edema that thickens the lung tissue through which the oxygen has to diffuse. Both estrogen treatment and age cause other inefficiencies in oxygen transport and inefficient use in the tissues, further exacerbating the shortage of oxygen. Interestingly, recent studies show that "capitulation stress" causes the same variety of problems in oxygenation, transport, and use. In stress, even the respiratory center of the brain becomes under-active, tolerating the state of hypoxia. Since progesterone activates the respiratory center, the depressed respiration of stress is consistent with a deficiency of progesterone.[†]

When tissue oxygenation is inadequate, glucose is depleted quickly. In prolonged stress, the liver's gluconeogenic response to the glucocorticoids is depressed, as is its ability to form and store glycogen. As glucose is less available, the amount of adrenalin in the blood rises, and fat is mobilized from storage as a substitute source of energy. Free fatty acids, especially unsaturated fats, are toxic to the mitochondrial respiratory system, blocking both the ability to use oxygen and the ability to produce energy. The increased use of fats, instead of glucose, causes lipid peroxidation to increase, and promotes the release of lysosomal enzymes, the accumulation of calcium in mitochondria, the depletion of ATP and creatine phosphate, and a failure to "pump" calcium out of the cells, causing incomplete relaxation and rigidity of the heart muscle cells.

This complex of effects can be called "catecholamine toxicity." Rona, et al.,[1] using isoproterenol in 1959, clearly established the existence of this toxicity. Several years ago, it was noticed that mortality in the U.S. from asthma increased greatly in the years since catecholamine therapy became common, without a corresponding increase in the incidence of asthma. It is now widely accepted that the therapy caused the increased mortality. Following Rona's work as it did, this large medical experiment can be taken as strong confirmation of the idea of catecholamine toxicity,

[†] The consistency with which oxygen becomes deficient in aging, stress, and estrogen excess suggests that a basic coordination mechanism may be involved, in which there is a shift toward the conditions which will activate the expression of certain genes—possibly the hypoglycemia-stress-heat-shock proteins, or possibly simply the proteins of cell division and growth.

and as a step in understanding stress sickness. Glucose depletion leads to adrenalin secretion, which causes fat mobilization, calcium-activated over-stimulation of cells, with impairment of the energy production which is necessary for recovery (by way of muscle relaxation and calcium excretion, etc.).

Broda Barnes showed that hypothyroidism causes heart disease, and also causes a tendency toward hypoglycemia. Low thyroid people compensate for the deficiency of energy and glucose (and of oxygen, for reasons similar to those mentioned above) by secreting an excess of adrenalin. Their 24-hour urine metabolites of adrenalin sometimes are 30 or 40 times normal. Recent studies that show that a moderate dose of thyroxin lowers lipid peroxidation confirm that thyroid has an anti-stress effect. The "conduction block" which occurs in hypothyroidism seems to be the same as the conduction block which develops in stress and predisposes to fibrillation. The electrical instability of the heart produced by excessive adrenergic stimulation can also make the sinus pacemaker more susceptible to vagal inhibition. (I think this effect can be observed in the skipped beats often experienced by hypothyroid people during stress or fatigue. In other situations, of long and intense stress, vagal stimulation protects against fibrillation.)

In hypothyroidism, there is impaired relaxation of muscles, as seen in the Achilles reflex, or in the T wave of the electrocardiogram. This is similar to the contractural rigidity which develops in the stressed heart.

When stress is severe and prolonged, the liver loses enzymes of the detoxifying system, and also of the system that forms bile acids, causing a tendency toward abnormal lipid metabolism, including hypercholesterolemia. Thyroid deficiency limits the consumption of circulating cholesterol for steroid hormone synthesis, and both stress and hypothyroidism are associated with elevated blood cholesterol. Considering the clear and well-defined toxicity of adrenalin and free fatty acids, the role of cholesterol in heart disease begins to look sort of epiphenomenal.

Fats enter and damage cells that are over-stimulated and de-energized.

Calcium is a universal activator, but excess calcium is the central link in most types of cell damage. Calcium uptake and retention are promoted by adrenalin, histamine, vasopressin, energy depletion, and lipid peroxidation and by the activity of phospholipases; since calcium can activate phospholipases and lipid peroxidation, and interferes with

energy production, vicious circles can develop. Excessive adrenalin and calcium also promote clotting, and—as the beta-adrenergic receptors become desensitized—spasms in the coronary arteries. Altered blood vessel tone, which can be produced by serious stress, can cause venous pooling of blood, which synergizes with the impaired relaxation of the heart to cause cardiogenic shock.

There are several systems that oppose the toxic effects of adrenalin. GABA, dopamine, and adenosine have multiple anti-adrenergic effects. In many situations, the parasympathetic system is protective against adrenalin. The protective steroids also act at many levels. Magnesium, retained in the cell largely under the influence of ATP and thyroid, is our basic "calcium blocker," or calcium antagonist. GABA and dopamine inhibit the ACTH-glucocorticoid system, and shift the steroid balance toward the protective anti-glucocorticoids, progesterone, testosterone, pregnenolone, and DHEA.

Adequate glucose and oxygen are the most important anti-stress substances. "Overload" of an organ means that the blood isn't delivering enough oxygen and glucose to sustain the needed level of functioning. Thyroid and progesterone tend to prevent overload by increasing respiratory efficiency, and by increasing the liver's glycogen storage.

Uridine, a co-factor in glycogen synthesis, can also prevent stress by improving glycogen storage.

Anti-oxidants, especially vitamin E, prevent tissue damage by promoting normal oxidation.

Selye's demonstration of corn oil's toxicity to the heart is an important link in the general picture of stress injury and adrenalin toxicity. The protective effects of saturated fats are not surprising when seen against the background of the toxic effects of adrenalin, causing the mobilization of fatty acids and the resulting lipid peroxidation.

Meerson's demonstration that gentle adaptation to hypoxia (similar to treatment with thyroid hormone) can prevent heart damage from subsequent intense and prolonged stress, is similar to Seligman's discovery that rats can be protected against stress by an experience of escape, but Meerson has surveyed a great range of protective processes, ranging from the subcellular level to the most highly evolved brain systems. In thinking about Meerson's achievements in protecting the heart against stress, it is important to remember that the heart is our most stress-resistant organ, and that the things that protect the heart from deadly

stress will also protect the other organs from the everyday stresses, which accumulate to cause the problems of general aging. Liver, lungs, pancreas and other essential organs are susceptible to the same kinds of damage as the heart, but under conditions that are relatively mild and ordinary.

The resistance of the heart and liver can be compared in several ways. For example, DNA replication is more easily suppressed by stress in the liver, than in the heart, but DNA repair is not affected in the same way by stress. Hyperfunction of the heart stabilizes DNA against injury, so DNA repair is greater in the liver than in the heart, and is least in the brain.

Meerson's laboratory has studied the anti-stress and anti-adrenalin effects of GABA and its metabolite, gamma-hydroxy butyrate, especially in the form of the lithium salt. (Lithium seems to have its own anti-stress effect, probably partly as a sodium agonist, and partly through its ability to complex with the ammonium which is produced in the brain in fatigue, which is exactly when the GABA system becomes active.) GHB is protective against stress damage to many tissues. It prevents stress-induced enzyme leakage from tissues, ulceration of the gastric mucosa, lipid peroxidation, epileptic seizure, damaged contractile function of the heart, and cardiac arrhythmias produced by stress or ischemia.

Meerson's group has also studied the protective effects of the gamma-butyrobetaine derivatives of the sort that are normally produced in the brain and heart, or that have been synthesized or extracted from plants. These substances stabilize the heart rhythm in acute myocardial infarction, and also in postinfarction cardiosclerosis.[2, p. 173] They have a protective action against both adrenalin and calcium. Interestingly, atropine potentiates the protective effect of the butyrobetaine against calcium toxicity.

A complete list of protective nutritional chemicals and natural drugs or analogs to our endogenous protective factors would be very long, but we should give special thought to certain ones, including succinic acid, which stimulates respiration and protective steroid synthesis; thyroid and vitamin E, which promote normal oxidation while preventing abnormal oxidation; magnesium; sodium and lithium, which help us to retain magnesium; tropical fruits, which contain GHB; coconut oil, which protects against cardiac necrosis, lipid peroxidation, hypothyroidism, hypoglycemia, and histamine damage; valium agonists, natural anti-

histamines; adenosine and uridine. Visits to higher elevations, and exposure to bright, long-wave light, can cause the body to optimize its own anti-stress chemistry. Avoiding the sense of being trapped is a high-level adaptive factor.

The life-span of cell organelles, DNA, and essential enzymes, is extended by adaptation. The cellular (membrane phospholipid) composition adjusts toward a lower content of unsaturated fatty acids.[3] Diacylglycerol causes activation of transcription, cell growth, and proliferation.[4] Stabilization of mRNA splicing and protein synthesis[5] suggests the possibility that this system might also be important in viral immunity.

P.S.: Pavlov's turn-of-the-century work on the heart's "trophic nerves" should be re-examined in the light of this new information on the trophic effects of adaptation.

Response to Dr. Davis

Townsend Letter for Doctors, November, 1995

THANKS for passing on the comments from Dr. Davis, PhD. I haven't received his letter asking me for references, and I assume it's because my Mexican address was listed with the coconut oil article. (I'm back in Eugene, Oregon).

Davis mentions that he looked in Medline for references to the animal studies I wrote about. Practicing physicians, who put in long hours with their patients, and who work in the context of an often authoritarian profession and an oppressive bureaucratic culture, need to find out in an efficient way what other physicians are doing, and they probably find Medline and Index Medicus very useful. But for a research scientist working in a college of natural sciences, in a university with a good library, there are more appropriate ways to search—especially since I emphasized that some of the work was done more than 50 years ago.

I decided to take a random sampling of Medline's information. (I noticed that the library's machine advised that Medline not be used if you are looking for information on non-human animals). I looked at their entries for 1984, where I found F. Bershauer, et al.:[1] "[Fat content in the coconut oil fed animals, after only 34 days, was 15.9 %; in the control group, 18.6 %; and in the sunflower oil fed animals, 21.1 %]."

So, I saw that Medline does include an animal-nutrition journal, and decided to check another year. J. Yazbech, et al.[2] suggested that the observed increase in resting metabolic rate produced by using coconut oil to create an essential fatty acid deficiency, is partly the result of increased heat production in the brown adipose tissue. The weight of that fat decreased by 28 %, while its ability to produce heat increased 69 %.

If Davis checked a data-base that was designed for animal research, he could find an abundance of publications relevant to the question of coconut oil's effect on body fat. I don't know of any computerized data systems for biology that go back 60 years, but manual searching of the printed sources is only a little slower than the electronic method, and infinitely more precise. Over the years, I have noticed that science libraries seem to be off limits to most professors, so any information they can get from computers should be significant, but the reliance on

computer-retrieved information puts an awful burden on the people who choose the keywords.

The *Townsend Letter*, especially with your new title, is obviously a journal of viewpoint, and not of technical data. As such, much of its function is to clarify goals, orientations, and beliefs, and possibly to encourage people to have more imaginative, flexible, and critical attitudes toward medical ideas. When a publication purports to be objective and "scientific," then there is a problem with unsupported assertions. If Davis had complained, for example, that an article in the *Scientific American Science and Medicine* by D. V. Spicer and M. C. Pike[3] was doctrinaire, ideological, and promotional, and failed to support most of its important assertions, I would think his letter was constructive. But I think he misunderstands the *Townsend Letter*'s reason for existence. Although it isn't at all the sort of "alternative health" journal I have imagined publishing, its openness is important in this increasingly repressive medical-bureaucratic environment.

The refereed journals are not great critics of themselves. Some appalling things happen at the "great journals," but the scientific-medical reader generally assumes that the editors fairly select representative experts to review the submitted work. Venality, bigotry and plagiarism are probably just as well represented in the main-line professional journals as in other parts of our society. The greatest abuses are possible when the referees are anonymous. A series of shocking experiences with journal referees over a period of 15 years led me to stop submitting my work to professional journals in the U.S. There are only a few small journals that I think are respectably free from the corrupting influence of corporate power.

In 1981, I began a newsletter to keep my friends informed of my progress. Occasionally, these almost private communications get wider distribution, as when the *Townsend Letter* picks them up. I am glad to offer a few readers some background sources and occasionally some additional material I didn't cite in the newsletter, but when someone is making their first approach to an area of research, I think the best method is to ask a science librarian to help them.

Response to Recent Pop-Medicine Articles on Progesterone Therapy

Townsend Letter for Doctors, 1984

SINCE 1940, it has been clearly established that estrogen is carcinogenic in every species studied. Shortly thereafter, studies appeared suggesting its possible involvement in heart disease. In 1950, I heard physicians warning about the risk of cancer when estrogen is used medically. The increased use of estrogen in the face of such evidence is, I believe, a process unique in medical history and is nothing but shameful for all who are involved.

By 1950, many studies had demonstrated that progesterone can protect against the effects of estrogen, including cancer. By that year, progesterone was shown to prevent estrogen-like and testosterone-like actions. Often, they suppress the formation of progesterone in the body, and in such cases could be called "anti-progesterone progestational agents." There is no justification for confusing progesterone with any synthetic steroid. When someone with access to the data confuses them, we must suspect their motives or their qualifications.

Progesterone has a unique position in physiology, partly because of its intrinsic range of hormonal activity and partly because it serves as a precursor for all the other types of steroid hormones. The concentration of progesterone which occurs during pregnancy is uniquely high among all hormones and requires a balance of intrinsic properties such that the physiology of the organism is protected, rather than thrown out of balance, by such high concentrations.

In spite of the toxic effects of even natural estrogens, multiparous animals and humans have a lower cancer incidence than do nulliparous individuals and apparently a longer life expectancy. These effects have all been related to progesterone.

Opponents of progesterone therapy are searching for new strategies, in addition to the standard "it's all in her mind" approach to women's symptoms. The ideology that pregnancy is a disease is being brought into service in this new conflict—women are being threatened with the thought that progesterone will make them feel pregnant, as if healthy pregnancy should cause undesirable feelings. One of the oldest warnings, and probably the most interesting, is that progesterone can produce

feelings of euphoria. Less amusing is the totally false new threat that women may become progesterone addicts.

Reading some of the anti-progesterone literature gives one the impression that many doctors are suddenly going to reject the use of any medication which requires the adjustment of dosage to suit the patient's response. After discussions of how unscientific it is to use progesterone in dosages varying between 200 mg and 2000 mg per day, a writer in *Medical Month* says that: "…Absence of standard dosages troubles observers on both sides of the therapeutic fence. 'It's trial and error,' says Nathan Kase."[1]

Just to the left of that quotation, there is a half-page advertisement for a tranquilizer, saying "Trust Tranxene," which comes in scored tablets of 3.75 mg, 7.5 mg and 15 mg, and in 22.5 mg "single dose tablets." A scored tablet of 3.75 mg suggests a possible dose of less than 2 mg, and a "single dose" 22.5 mg tablet indicates a dose about twelve times larger. This article, *Dangerous Fad Therapy for Premenstrual Syndrome?*, defines progesterone as "cholesterol derivative," very likely to get a little extra propaganda value from associating it with the cholesterol scare. In fact, all natural steroid hormones are derived from cholesterol. (I wonder how such a sleazy article as this finds its way into physicians' waiting rooms.)

A new pseudo-medical campaign is under way, against the use of natural progesterone therapy in premenstrual syndrome. This campaign is likely to intensify as new, efficient and effective forms of progesterone become available.

Response to Tim Zell

Green Egg, Volume 5, Issue 51, 1972

I have just read *Green Egg* 44, and have comments on several things in it. Immortality of the body will resolve the disputes about what constitutes survival of the personality. To achieve it, we have to know what the "intrinsic" causes of bodily deterioration are, inaging. When growth stops, most differentiation of cell function stops, and soon dedifferentiation and cell death begins. Anything that interferes with energy production promotes the process: damage leads to thickened connective tissue, which limits diffusion of oxygen, which causes more damage. In youth and health, cell water is "liquid-crystalline," or ordered, and this order causes the "cell sap" to retain potassium and exclude sodium. Anything that lowers the energy charge of the cell causes the water to "melt" or become disordered. When dedifferentiation is complete, division is all the cell can do: wasting from cell death, and cancer are two outcomes of "aging." Progesterone and testosterone, two very similar female and male hormones, promote differentiation. Estrogen (men have about as much as women do except for a peak following ovulation) dedifferentiates, and promotes all the known processes of aging.

Experience modifies cell water (especially in nerves), and so is intimately involved in development of tissue: a stimulating environment causes brain growth in rats, body ratio correlates with a long brain/ Acquired brain size happens to be inheritable, at least in rats. (These data are all American, published in the most respectable journals. The Russians for a long time have had an attitude toward matter—even in the 19th century—that makes them more respectful than the average Western person of the abilities of matter and organisms, and better able to have richly varied perceptions about nature. The mechanistic-Cartesian western tradition of science tries to dominate "passive matter" and distains, ignores, or steals the real achievements of the Russians whose claims to have invented just about everything turn out to be true, if you study sources rather than western review articles.)

These data (and many more) imply that "culture," in a very specific sense, reflects and limits bodily evolution, development and life-span, as well as having its more obvious affects on consciousness and behavior. Discovery and high generality of knowledge contribute to renewal of the

body bodily flexibility and sensitivity are an aspect of "high generality of knowledge." Cellular, behavioral, and intellectual complexification require participation in a richer culture. Sexuality is an important part of this evolution-for-survival: consider the idea that orgasm is always a discovery-perception of newness. The minimum immortal unit is apparently a sexual-intellectual couple. There are vitamin-mineral-hormone-manipulation technologies that delay aging, but awareness is essential to stabilize the complexification.

Instead of eugenic selection, we are left with the personality more complex and rewarding responsibility for growth.

It is probably through modifications of cell water that attitudes can change enzyme function, response to drugs, intensity of consciousness, etc. Palladin, a famous Russian enzymologist, has shown many effects of awareness on enzyme activity.

Kozyrev's ideas on time and organismic "handedness," etc., are probably closely related to the microstructure of cell water. Incidentally, the hemispheric spin effect is mostly mythical: it was only recently that someone finally managed to design a very big, highly insulated vessel that would consistently show a hemispheric spin; the bathtubs etc., depends on shape of the tub, small currents, etc. a good example of how a good theory can persist in spite of many years of non-confirmation. Dror Sadeh, while working in Washington, DC, did some experiments that confirmed Kozyrev's "wildest" suggestions. He mounted a cesium clock on a truck and compared its signal with that of a fixed clock in Washington; as he drove up and down the coast, the distant clock showed a "red shift," corresponding to 1500 miles (he went as far as Maine, about 1500 miles away). The distant clock operated more slowly, or radio distance altered the frequency of the radio signal; the effect began at sun-rise, and continued through the day; he observed a similar effect in star-light passing close to the sun. This spoils the red-shift argument for the expanding universe, and also changes the probable meaning of the circumnavigated cesium clock that was supposed to confirm the existence of a relativistic "twin (or clock) paradox." They support Kozyrev's contention that time is a form of energy and organization (negative entropy). There is a developing link between these ideas and those of the Russians who maintain that telepathy and PK use a kind of energy that is not electromagnetic. H. C. Dudley is working on the implications of a universal, isotropic "neutrino sea," which among other

things forms a link for nuclear interaction at a distance, and serves as an "ether" for transmission of electro-magnetic energy. Nuclear decay, for example, turns out to be an equilibrium process not a "constant," and is subject to alteration by such things as molecular order. His most recent work will appear in the physics journal *Nuovo Cimento* soon.

The Kirlian effect itself doesn't seem to involve anything but a visualization by a high frequency alternating "corona discharge" of conductive regions in and around the organism; an understanding of the conductive medium electronic resonance, or "neutrino sea," or whatever is a problem that has been recognized by many others. Hormones, radiation, emotions, etc., cause such changes of tissue conductivity and charge distribution, that can be detected with a Burr microvoltmeter or more common instruments.

If we can avoid a compulsive answering too-soon, and assimilate a very great variety of experiences, high generality interpretations will eventually become possible.

Rosacea, Rhynophyma, Pterygium & Riboflavin---& Varicose Veins

Townsend Letter for Doctors, July, 1987

SEVERAL times lately I have heard that the cause of rosacea is unknown; for example, in Dr Donohue's newspaper column, he wrote that "we don't know the precise cause," but then said that "hot beverages and spicy foods can contribute to such enlargement; so does alcohol." For many years I have assumed that the cause was known to anyone who cared to know, so I think it might be useful to describe some case histories, and some processes that relate to the cause.

In 1964 a somewhat alcoholic neighbor of mine was interested in improving his memory, since he had trouble finding the words he wanted when speaking or writing. His nose was remarkably red, but at the age of 41 or 42 it was not noticeably enlarged. I suggested many times that riboflavin might help, since I inferred from his very vascularized nose that his tissues were experiencing relative hypoxia, and that his brain tissue might be suffering even more than his nose, since such extensive new growth of blood vessels would seem less likely throughout the brain. For several weeks, he kept coming back asking me to remind him what it was that I had suggested; I started giving him notes, but he mislaid them. Finally he retained one of the notes long enough to ask his doctor to give him some vitamins, and the doctor prescribed daily injections of the vitamin B complex. I saw him in the afternoon a few hours after his first injection, and was surprised to see that his nose was no longer red; he spoke fluently and quickly, and did not have to search for words. Each day that week he returned for more injections, and both his nose and his memory stayed healthy. However, over the weekend, when the doctor's office was closed, both problems returned in full: his nose was as red (and shiny) as ever, and he struggled for some word in almost every sentence. By Monday it seemed that he had forgotten the whole episode, and didn't return for more injections.

I moved away around that time, and didn't see him again until 1976. At that time, his nose didn't seem particularly red, but it had enlarged and become very lumpy—a potato nose, or rhynophyma. (Rhynophyma is considered to be an advanced, hyperplastic form of rosacea.) He had

undergone surgery for defective heart valves, but seemed to be in good health except for occasional nosebleeds. (He died in 1985.)

Before learning that he had nosebleeds, it had occurred to me that bloodshot eyes and a red nose probably have internal equivalents, which might be revealed as nosebleeds in some individuals, and as strokes in others. I knew a woman whose four year-old son had very frequent nose-bleeds that usually occurred around one or two AM during sleep, or during daytime naps. He also had frequent violent rages, that seemed to happen after he had eaten certain foods, usually cookies or cake. I reasoned that a riboflavin deficiency would waste glucose by blocking mitochondrial respiration, and that blood vessels would dilate to deliver more blood to the tissues. Since blood sugar falls at night, I thought this could account for the regularity of his night-time nosebleeds. His frequent angry behavior seemed to be an exaggeration of the normal irritability of hungry children. His mother had some distinct mental problems, which had included a classical postpartum psychosis. She wore contact lenses, and I noticed that she had chronically visible blood vessels in her eyes, mainly on the side toward her nose. The area was yellowed, and lumpy. Close inspection suggested that the vessels had become increasingly enlarged, numerous and tortuous, until the surface of the eye was distorted by the excess of blood vessels.

The cornea normally has a high concentration of riboflavin, but it is very susceptible to a deficiency of that vitamin. It receives its oxygen largely directly from the air, and partly from the ring of blood vessels at its edge, which are supplied by vessels approaching from the two sides. In her case, it seemed that the contact lenses, shutting off direct contact with the air, had led to an invasive growth of blood vessels to the edge of the cornea, probably partly because of a riboflavin deficiency.

I think this would be called a pterygium, but I think the same kind of process would be called rosacea if it occurred on the nose or cheeks. Oxygen deficiency causes connective tissue cells to produce extra collagen. This would intensify the problem of delivering oxygen to the cells, tending to set up a vicious circle. Even normal levels of riboflavin and other nutrients and oxygen in the blood wouldn't be enough to allow the necessary amount to reach the cells, once the lumpy fibrous overgrowth had begun to develop.

I gave the woman and her son each 10 mg of riboflavin one morning, and suggested using that amount for a few weeks. The boy's nose didn't

bleed that day or in the night, and as far as I know, it never bled again. He stopped having his fits of rage. Several years later his mother became chronically insane; I believe her heavy smoking, a poor diet, and an increasing hormone imbalance, were probably causing an increasingly severe energy deficiency in her brain. In that organ, as in the heart and lungs, androgenic steroids and other anti-glucocorticoids such as progesterone, are probably responsible for a normal resistance to atrophy during starvation. However, girls suffering from anorexia nervosa do sometimes have demonstrable shrinkage of the brain (which can be reversed by good nutrition) showing that the brain is not absolutely protected from catabolism, especially when the steroid hormones are out of balance.

The brain seems to be extremely resistant to the overproduction of fibrous tissue, unlike the exposed tissues of the eye and nose. There are some degenerative brain diseases, though, in which the supportive glial cells are overproduced. This may represent a basic stress-reaction, not so different from that which occurs in potato-nose and pterygium.

Although I have seen nearly instantaneous effects of a small dose of riboflavin, I want to emphasize that the enlarged and invasive blood vessels caused by a deficiency of that vitamin will not necessarily go away even with prolonged supplementation with riboflavin. I believe that the delicate red blood vessels that often first appear around the nostrils, and the larger red, purple and blue vessels that usually appear on the sides of the feet below the ankles, and more obvious varicose veins, can also result from loss of tone in the walls of the blood vessels, in addition to any overgrowth process that might be occurring, and that various problems related to stress and nutrition can be responsible. I have seen very distinct blood vessels disappear completely after using thyroid and oral DHEA. I think this is partly the result of restored muscle tone, as can sometimes be seen in the blood vessels of the hands shortly after taking progesterone.

Many people who have taken a course in physiology think that arteries and arterioles are the only blood vessels containing smooth muscles because of the odd over-emphasis that is usually given to the contraction of arterioles. In fact, I feel that the conventional theory about the role of arterioles in regulating circulation is wrong. It is usually assumed that the capillary wall and the endothelial cells are not contractile, and this

idea, with the assumption of passive veins, creates the impression that "peripheral resistance" is only the result of arteriolar tone.

Many veins are very well-supplied with smooth muscle. When the physician scoffs at the idea that varicose veins could "recover," it is because of the idea that "they occur when the valve fails." Since the valve is just a flap of tissue, it is hard to imagine how it could be restored. But if you realize that veins (especially the subcutaneous veins which become unsightly varicosities) are well-muscled, you can see that a loss of muscle tone will lead to swelling of the vein, and that a valve which could close a small channel, simply can't reach across the channel of a distended vein. That is, valve failure will necessarily follow loss of smooth muscle tone. If the tone is restored, the channel will return to its normal size, and the valve would have a chance to function again.

Although major structural restorations can occur in many tissues, even in middle-aged people, when conditions are favorable, it is much better to stop degenerative processes before they have gone very far, by optimizing all aspects of the environment, as far as this is possible.

(Synthetic riboflavin is allergenic, so natural sources are the safest.)

Sales Pitch for Linseed Oil

Townsend Letter for Doctors, February/March, 1989

YOUR publication performs an important service in allowing the free expression of ideas in medicine and related subjects. Many publications, contrary to the spirit of science, "protect" their readers from improper ideas. Too many publications are actually protecting their advertising revenue by rejecting criticism of certain drugs or food supplements. Industries with annual profits in the billions of dollars have the power to control medical journals, professors of medicine, and public opinion. *Townsend Letter for Doctors* is one of the few publications which has allowed criticism of the idea that our diet should be supplemented with the essential fatty acids.

The article in your December issue by Mike Minarsich, and the book review excerpt by J. S. Bland, Ph.D. call for some special criticism. Minarsich is obviously a linseed oil salesman (president of New Dimensions Distributors), and he takes his pseudo-facts right out of the book by Udo Erasmus, so my comments are mainly about the Erasmus book, and some of its ideas which are derived from the "scientific work" of Johanna Budwig.

Dr. Bland's review excerpt says "Fats and Oils is filled with interesting and accurate information…" and "is the first complete guide to everything you need to know about fats, oils and cholesterol to make the right food choices for your health." T. H. Huxley said that book reviewers too often get all their information on the subject from the book being reviewed, like the Abyssinian who supposedly took his steaks from the same ox he was riding; but it is hard for me to believe that Bland has really read this error-filled, incompetent, and possibly deliberately misleading book. If Udo Erasmus is a hired commercial writer working from information provided by his employer, then he has done a smoothly competent writing job, and it is the publisher who misleads by failing to give some background information.

Judging by the book, I suspect that neither Erasmus nor Budwig has studied the fundamentals of organic chemistry. That isn't important. But it is very important that linoleic acid, and related oils, in the amounts recommended by Udo Erasmus, are known to cause:

- impaired brain development and learning;
- damage to skin and bones;
- accelerated aging and age-pigment accumulation;
- damage to the circulatory system;
- increased cancer incidence;
- suppressed immunity;
- endocrine dysfunction.

U.S. consumption of seed oils had been almost doubling every decade since the first world war, but the technological advances of the 1960s which allowed paints to be made from petroleum derivatives, rather than from linseed oil, safflower and soy oil, stimulated the redirection of large amounts of these substances from paint production into the food market. Clever marketing tricks are in some cases creating price mark-ups of 10 000 %. I spoke to a dealer who said he recognized the toxicity of linseed oil and wouldn't use it himself, but that the profit was so big he was going to keep selling it.

An acquaintance who died recently after several months of eating large amounts of linseed oil told me that it had been used by both W. F. Koch, M.D. and Max Gerson, M.D. I knew this wasn't true: For example, Gerson's program evolved from a diet for migraine and tuberculosis into a cancer therapy, and involved the use of thyroid extract, liver, fresh juices, and a little butter, but over and over he said "absolutely no oil."

My friend sent me a page from Gerson's book, containing the recommendation for 1 tablespoon of linseed oil. My copy of the Gerson book, published while he was alive, contains no such statement on that page, but rather the phrase in bold capital letters, NO OILS! My informant also assured me that Gerson had known Budwig and respected her work. Gerson's book contains detailed discussions of all the main dietary approaches to cancer, with a large number of references to the scientific literature, and it did not mention Budwig at all. Since Budwig's proposals are diametrically opposed to Gerson's he would have had to account for them if he had known of them.

The people who are using Max Gerson's name and reputation to sell linseed oil are harming the people they mislead, and are dishonoring Gerson's important work. The altered book is going to boggle the mind

of any thoughtful student who tries to understand what Gerson was really doing.

Minarsich and Erasmus similarly invoke the names of several great biochemists in making their sales pitch for linseed oil. Any serious student of biochemistry will recognize the absurdity of their outline of biochemistry, but the average reader is likely to swallow the idea that Ms. Budwig represents the culmination of a century of scientific progress. Dale Alexander made a career of the idea that cod liver oil will grease arthritic joints. Now a generation later, the vast food oil industry has a slightly higher class of sales promoters. It is urgent that we start developing a more critical medical-scientific culture.

Research showing the toxic effects of unsaturated oils goes back more than 60 years. A 1985 article published in my newsletter cites some of the key references.[1, p. 41] These substances inhibit many enzymes (e.g., in digestion, in immunity, in clot removal, in thyroid function), they disrupt mitochondrial energy production, and they interfere with communication between cells. We hear very little about these toxic effects, and there is not much money available for more research in these areas. Naturally, these topics aren't mentioned in the Erasmus book. The "toxicity" questions treated in the book do not include the toxicity of fresh and natural unsaturated oils, and so they have the function of a red herring, distracting the reader.

For nearly 20 years, mainline medicine has advocated the use of unsaturated oils "to protect the heart." A few scientists, like Hans Selye, kept telling the (contrary) truth. Now big business has many people in "alternative medicine" falling for the false establishment story.

Sharks, Salmon & Osmotic Therapies

Townsend Letter for Doctors, July, 1991

In the 1960s, I met Leonell Strong, the geneticist who developed a famous strain of mice that are extremely susceptible to breast cancer. My first research in endocrinology had to do with their estrogen metabolism, and ways to normalize it. Strong (who studied genetics with T. H. Morgan) was interested in the fact that sharks are not susceptible to cancer. As a geneticist, he saw this in relation to their "genetic stability," that is, the fact that they haven't developed beyond an early stage of evolution, and he believed that cancer is a result of genetic instability. He found that injections of an extract of shark's liver prevented mice from developing breast cancer; however, similar extracts from other kinds of liver had similar effects on the mice. Since his mice had too much estrogen, I supposed that their livers were deficient in something needed to eliminate estrogen, since the liver normally is a powerful regulator of estrogen, using a certain system of "detoxifying" enzymes. (As it turns out, the thyroid hormone is the basic regulator of this detoxifying function.)

As I studied estrogen in other situations, two features of its action stood out—it interferes with respiration, and it causes cells to take up water. Its other effects seem to follow from these. In the 1920s, it was found that hypotonicity, an excess of water, stimulates cell division (while hypertonicity inhibits it). Around 1940, Hans Selye found that estrogen's systemic effect mimics the shock phase of the stress reaction. In shock, deficient circulation of blood and thus deficient oxygenation of tissue are the main problem, and Selye considered the adrenal steroids to be crucial in resolving the problem, and creating adaptation to the stress. But the adrenal steroids can have their own undesirable consequences.

Sharks, besides being primitive and not suffering from cancer, are physiologically unique in another way: their body fluids are osmotically in balance with seawater, making them hypertonic to other animals' body fluids. The mineral content of sharks' blood is not very different from that of other animals. The osmotic difference is made up by a very high concentration of urea (and of trimethyl ammonium). In general, animals that live in water are able to get rid of ammonia easily, because it is very soluble in water, and the excretion of nitrogen as urea and

uric acid is considered to have evolved to avoid the toxicity of the large amount of ammonia that would otherwise accumulate in land animals. Therefore, it seems that sharks' urea evolved as a kind of osmotic buffer (rather than as an excretory product), keeping them in osmotic balance with ocean water, without having to deal with internalization of the extremely high (3.3 %) sodium content of ocean water.

Another kind of fish, the salmon, which return to fresh water for reproducing, show the other extreme of adaptation to an osmotic problem. After living "isotonically" in the hypertonic ocean environment, keeping their mineral content and osmolarity lower than sea-water's, they suddenly have to readapt to the extremely hypotonic fresh water. The secretion of prolactin and glucocorticoid steroids seems to facilitate this sudden adaptation, but those hormones also seem to produce an explosively rapid kind of aging. I think their condition is similar to the "Cushingoid" symptoms that frequently appear in middle-aged people.

Highly energized cells can resist the osmotic stress of too much water in their environment, and tired cells can't. Removing the stress, by making the surrounding fluid isotonic or slightly hypertonic, can protect the cells' energy level, and give them a rest. Until about 1940, the use of hypertonic solutions in therapy was fairly common. Books still mention the use of urea, USP, as a diuretic to treat brain swelling, but I haven't heard that it is still used this way in the United States. Veterinarians sometimes use hypertonic urea to treat uterine inflammation and infected wounds. Early in this century it was often mentioned as a safe disinfectant and promoter of healing for wounds. It was sometimes used as a powder, and was sprinkled pure onto skin grafts or between bone fragments in repairing fractures. Although it caused some pain, people generally thought it accelerated healing while preventing infection. (Typically, 5 g of powder would be dosed into the wound; milder treatments would probably have been possible, but wartime conditions didn't foster subtlety in medical research.)[1]

Hypertonic sodium chloride (Clifford White, *Lancet*, October 30, 1915) was also used to treat infected wounds, and its success in treating war wounds led to its use as a vaginal douche in treating various inflammations and infections, including infections associated with childbirth, salpingitis, cellulitis, gonorrhea, vaginitis, and erosions of the cervix, and in preparing a cancerous cervix for surgery. Irrigation of the abdomen with the saline solution gave good results in acute infections

that required abdominal drainage. White used a solution containing 1/2 ounce of sodium chloride and 1/16 ounce of sodium citrate in a pint of water. M. Englaender[2] used intravenous injections of 100 mL of 2 % NaCl to treat a variety of infections and inflammations.

In Russia, Gubin[3] treated sciatica with two glasses of warm water containing 1.4 teaspoonfuls of NaCl, placed in the rectum; it caused profuse sweating and diuresis.

I have known many people with food allergies (or with lingering cold or flu symptoms) who said that although their abdomens were distended and uncomfortable, they were so thoroughly constipated that no laxatives worked. When their bowels did move, they sometimes described ribbon-shaped feces. Occasionally I saw their X-rays, in which an opaque "meal" showed up as a very thin and intermittent filament. It appeared that the wall of the bowel was enormously swollen. One woman complained that enemas were useless, because when a quart of water was injected, nothing returned from the bowel, though she would have to urinate more than usual. The colon was obviously drinking the water. I suggested that she try a hypertonic glucose and salt enema, with an aspirin added, neutralized by a little soda, and she immediately had good results.

People with less complete obstruction can get the same effect by drinking a hypertonic solution of epsom salts and sodium chloride, with an aspirin. Although this osmotic deflation of inflamed tissue is crude, I think it helps to promote real recovery, by reducing the reactivity of the tissue, and allowing it to recover its normal energy patterns.

In PMS, edema is a common problem, and it used to be thought that edema of the brain was responsible for the irritability or depression or other nervous symptoms, and diuretics such as ammonium compounds and urea were commonly used. (Premenstrual salt cravings are the result of the estrogen-disturbed water balance, and salt-restriction for PMS is as inappropriate as it is for pre-eclampsia or toxemia of pregnancy.) Alkaloids are often active in modifying the water content of physical systems, as well as of cells. The alkaloids that are often used in treating PMS seem to favor improved oxygenation and elimination of edema. I suspect that these drugs, and the natural hormones progesterone and pregnenolone, act in the same direction as hyperosmolarity.

For several years, I have been interested in the biological effects of ammonia, and compounds that are metabolically close to it. There is

clear evidence of ammonia's antiviral effect, which stimulated extensive research by drug companies seeking patentable antiviral amines. Most simple substances have regulatory functions in themselves, besides participating in other systems. Besides viral immunity, I think ammonia is involved in regeneration and nerve modulation. Urea, inosine, GABA, the polyamines, and betaine derivatives (e.g., gamma-butyrobetaine) are closely related to ammonia metabolism, and combinations of them will probably have many useful biological effects.

Sodium chloride, glucose, and other substances can be used at high concentrations for their osmotic effects, but they also have chemical and metabolic effects that aren't necessarily desirable. Both osmotic and biochemical effects should be taken into account in a given therapy.

Solving Some of the Problems of Aging

Townsend Letter for Doctors, January, 1991

In the 1970's a strange "Pine-sol" type disinfectant with insecticide was widely promoted in Mexico, and nearly every bathroom, bus, and public room in the country smelled of that rank, un-pinelike substance. One morning I woke around 3 AM smelling Pinosol, and as I was trying to decide where the smell was coming from, I realized that I could smell it only while exhaling—it was coming from inside me. From then on, I began to wake up every night, usually between 2 and 4 AM. I knew that many old people like to get up and start their day a little before dawn, but after this experience I began to notice that many younger people have—and are disturbed by—a similar alteration of their sleep rhythm.

Around the time of my Pinosol experience (in 1979) I happened to find a dead bug in my Nescafe bottle, and it occurred to me that this was the first bug of any kind that I had seen since I arrived in Jalapa. Walking to the outskirts of the town, where there were forests, I found a reasonable number of insects, but I couldn't find one in the city. This fact, combined with my awareness that my tissues were soaked with insecticide, (and other discomforts) caused me to quit my job at the university and return to Oregon. As I was driving across the desert, I noticed that I would smell Pinosol whenever it was meal-time. Apparently low blood sugar, causing fat mobilization, would cause the insecticide to be released into my blood. I had been back in Oregon for several weeks before I quit smelling it at meal-times and in the middle of the night. But even when I couldn't smell the chemical I kept waking around 3 AM, and I got in the habit of drinking milk or orange juice to raise my blood sugar enough to lower my adrenalin (and cortisol) so that I could return to sleep.

Since I had already spent years investigating the effects of light on hormones and health, I began to see that the existing knowledge regarding the involvement of stress and glucocorticoid hormones in the aging process meshed perfectly with my concept of "winter-sickness" and the role of inadequate light in the stress-related diseases such as the premenstrual syndrome, colitis, osteoporosis, and depression.

Besides looking for the precise ways in which light acts on us (such as by preserving the function of the essential respiratory enzyme, cy-

tochrome c), I also considered the dietary factors which might exacerbate the problem of light deficiency (such as an excess of unsaturated fats) and the possibility of other therapies, including drugs, that might be more practical and economical than hormone supplementation.

When various kinds of cells are deprived of energy (mast cells are often studied) they tend to produce (and secrete) histamine (among other substances). Unsaturated fats promote the release of histamine, while short-chain saturated fats, and glucose, inhibit it. When mice are killed by a variety of methods, they are found to have very high tissue histamine levels, so the high-histamine phenomenon seems to be about as generalized as shock. People who suffer from nocturnal asthma are known to have their highest blood level of histamine around 4 AM. Some inhibitory cells in the brain (including those involved in the "coma" state of protective inhibition) secrete acetylcholine. The similarity of the effects of histamine and acetylcholine are such that many people used to think of histamine as the "systemic cholinergic" hormone equivalent to acetylcholine. As a result of their similarity, any chemical which interferes with one of these "transmitter substances" is likely to interfere with the other, though not necessarily in the same way.

People who are awake in the dark have higher levels of cortisol than when they are asleep in the dark, that is, sleep is a partial defense against the stress of darkness. The cortisol (an adrenalin) secreted in darkness, or other stress, has the important function of maintaining the blood sugar level. The fact that cortisol causes the destruction of tissue to convert to glucose is the reason that stress and hypoglycemia are destructive. In 1971 I found that none of the sexually mature hamsters in our lab had any detectable thymus glands during the winter, though they all had them in the summer. Since estrogen and testosterone, the other thymus-shrinking hormones, are lower in the winter, I inferred that it was cortisone which caused their loss of thymus in the winter.

The main inhibitory "transmitter" substance in the brain is GABA (gamma amino butyric acid), which is closely related to aspartic and succinic acids. GABA has many anti-stress effects, besides the direct brain-quieting action. For example, it causes a sequestration of insulin, keeping some sugar from being turned into fat, and it promotes progesterone formation, which protects many systems from damaging hyperactivity.

Succinic acid was found by Szent-Györgyi to stimulate tissue respiration. Others found that it promotes the production of protective steroids, and more recently it was found to be the best material for chelating and removing aluminum from mitochondria. Succinic acid was identified as a major component of Vladimir Filatov's biogenic stimulators of tissue regeneration. Finding food sources rich in this material (especially in combination with the closely related butyric acid) would be desirable.

I experimented with various herbs known to have antihistamine and anticholinergic action, with the thought that they would help to sustain blood sugar through the night. (For example, insulin secretion is stimulated by acetylcholine from cholinergic nerves, and lowering its action during the night would decrease the need for adrenalin and cortisol.) My best results so far have been with a combination of the mildly sedative Jimson weed and the stimulant Ephedra; in combination, it seems that their antihistamine and glucose sustaining effects predominate, allowing comfortable sleep without the dry-mouth effect of their anticholinergic action.

It is now clear that both stress and an excess of the glucocorticoid hormones cause brain damage (as well as damage to all other organs). Marion Diamond's work with rats (confined or free) showed that stress causes very general brain damage, including to the cortex, and others have shown specific damage to the hypothalamus, the hippocampus, and other brain areas.[1] (Nerve cells are replaced by connective tissue cells. I think the damage is analogous to the viral (or "prionic") disease, scrapie; brain tissue from a scrapie infected young animal is antigenically similar to tissue from an old animal without the infection.)

Excessive cholinergic action in itself can cause brain damage.[2] The anticholinergic drugs, amantadine (Symmetrel) and atropine (related to the substances in Jimson weed) have been used to treat Parkinson's diseases. Atropine used to be listed as antidote for many poisons, probably because of its stabilizing effect on the nerves. It also promotes the formation of the protective hormone progesterone. Efficient energy production keeps the body from moving either to the "cholinergic" extreme or to the glucocorticoid extreme. When the mitochondria are damaged, the protective steroid pregnenolone (which is made in the mitochondria from cholesterol) can't be produced. In young people, the brain contains a very high concentration of pregnenolone and its derivatives, DHEA and progesterone, all of which stabilize cells and

protect against the effects of cortisol, but in old age these fall to about 5 % of their normal concentration, leaving the brain exposed to the destructive action of cortisol. The protective hormones can be used directly, or their synthesis can be promoted by using succinic acid, thyroid, vitamin A, and the atropine-type drugs, and maintaining adequate cholesterol. (T. Shimamoto, et al. have reported that low cholesterol is associated with a high incidence of stroke, especially hemorrhagic stroke.)

Since excessive excitation of cells (relative to the energy that's available) causes cells to die (in the brain, as elsewhere), it is important to consider as many of the natural means of inhibition as possible, while doing everything possible to sustain energy production. Succinic acid and butyric acid seem to be involved in both the energy sparing and the energy producing processes. The amino acids taurine and glycine are also considered to be inhibitory transmitters in the brain. Gelatin, which is extremely rich in glycine, is often added to fruit juice to take at bedtime as a sleep-supporting drink. Several of the local anesthetics including procaine and lidocaine, have cell-protecting action. Their anti-inflammatory or antihistamine function is probably caused by a more general cell-stabilizing effect. For example, lidocaine is used to prevent heart arrhythmia, and it can prevent tired heart cells from taking up too much calcium (which depletes cellular energy, in a deadly vicious circle). When taken orally at bedtime they act directly on the intestine (especially if there is inflammation anywhere in the intestine) to normalize its function, and even an occasional dose can have a long-lasting effect on the general health.

Estrogen, too, causes brain damage. Its prenatal effect on the brain has been known for many years. Marian Diamond found that estrogen, like the stress of confinement, causes the cortex and other parts of the brain to be smaller than normal; she also found that progesterone, opposing estrogen, enlarges the cortex.

It has been suggested that estrogen's nerve-damaging action is caused by way of elevated glucocorticoid hormones. (In the "hamster lab" where I worked, other people showed that estrogen causes enlargement and hyperactivity of the adrenal cortex.)

When I first suggested that "aging is estrogenic," or that estrogen promotes aging changes, it was because of a large number of biochemical similarities in aging and in the state of estrogen dominance, and the absence of any detectable biochemical differences between the states,

except their history.[3] For example, in both states the oxygen tension is relatively low, and as a result, unsaturated lipids are rapidly changed into "age pigment" or lipofuscin through lipid peroxidation.

Insomnia and hot flushes commonly occur around the time of menopause. These and other symptoms of menopause can be produced by an excess of cortisol, as in Cushing's syndrome.[4] The increase of cortisol during the night is probably responsible for "night sweats." When progesterone is deficient, cortisol—even in "normal" amounts—has a stronger effect.

The animal evidence is now clear, showing that it is largely the prolonged exposure to estrogen which causes reproductive aging.[5] Treatment with progesterone can prolong fertility,[3,6] as well as controlling symptoms such as insomnia and osteoporosis.

Until we know how to modify the environment (especially the radiant spectrum in the region of 600 nm to 1200 nm) to minimize the stress of winter and nighttime, the use of nutrition and hormone balancing techniques can control symptoms and minimize the cumulative damage that is occurring while we have the symptoms.

Some Effects of Progesterone in Men

Ray Peat's Newsletter, 2021

CLASSIFYING progesterone as a "pregnancy hormone" and a "female sex hormone" has seriously limited understanding of its function in both men and women. It is a stabilizer of cellular structure and function in all organs, similarly in men and women. This stabilizing effect is especially important in the nervous system, where it is protective against stress. In both men and women, a progesterone deficiency is associated with problems including seizures and bipolar disorder, irritability/elation, aggression, and depression, as well as sex-related problems.

In the 1970s, an acquaintance told me that he had become impotent following his vasectomy. I was familiar with the progesterone deficiency produced in women by tubal ligation and by intrauterine contraceptive devices, and I had seen a study of men's hormones following a vasectomy, in which an isolated deficiency of progesterone sometimes occurred, so he decided to try some progesterone. He later said that a single dose had corrected his erectile problem. Other young men with erectile dysfunction, from other causes, had similarly good results with small amounts of progesterone.

When a problem is quickly and permanently corrected with a small amount of progesterone it seems likely that the progesterone acted in the brain to shift the balance, maintained by endorphins, away from the stress induced inhibition of progesterone and testosterone synthesis. At the same time, though, that progesterone is lowering cortisol, it is also reducing inflammation, partly by acting as an antagonist to aldosterone. Increased aldosterone is associated with erectile dysfunction,[1–3] and it interacts locally as a testosterone antagonist. In this, and other situations involving testosterone antagonists (estrogen, cortisol, aldosterone), progesterone can have a directly testosterone-supporting effect.

After the age of 35 or 40, many men experience a decline in their resistance to stress, corresponding to the decline in protective substances such as DHEA and progesterone. Often a small amount of progesterone, 5 or 6 mg (for example, a drop of Progest-E the size of an unpopped kernel of popcorn) can make a difference, sometimes lasting for a few days or more. Paying close attention, the effects are usually noticeable within

about half an hour. At a certain level, progesterone can antagonize the effects of testosterone; in younger men, 2 or 3 drops can have that effect. That effect passes within a day of stopping the progesterone. If a younger man uses progesterone topically, for example for sunburn, a little olive oil should be applied to the skin first to make it spread easily; if it's used on a large area, the same anti-testosterone effect is likely to be noticed.

Steroids/Thyroid

Blake College Newsletter, Volume 1, Number 4, 19XX

Steroids

THIS type of molecule might be the most common carbon compound in the universe. It is made by single celled organisms, by plants, and by animals, and has many kinds of function. The steroid hormones are involved in all aspects of animal physiology, and overlap with control functions of the nervous system, peptide hormones, metabolites, prostaglandins, cyclic nucleotides, etc. Sometimes people speak of "steroids" when they mean glucocorticoids such as cortisol or a synthetic like dexamethasone, or, among athletes, when they mean anabolic steroids or synthetic androgens; and so it is common to associate "steroids" with harmful side effects. All foods contain steroids and sterols (a major type, containing an alcohol group and a side-chain), some of which are beneficial and some of which are toxic or allergenic.

In animals, cholesterol is the basic sterol molecule, which is massively converted into other substances, including the steroid hormones. Thyroid hormone and vitamin A are required for this conversion. The first step occurs in the energy-producing mitochondrion, where cholesterol loses its side-chain and is slightly oxidized, producing pregnenolone. Being less fat soluble than cholesterol, pregnenolone leaves the mitochondrion, so it can't inhibit its own synthesis. Rather, it seems to stimulate its own synthesis, though this isn't as clearly established as in the case of progesterone.

Depending on the tissue, pregnenolone will be converted by enzymes in the cytoplasm into either progesterone or DHEA (also called DHA, dehydroepiandrosterone). The fact that progesterone (and probably pregnenolone) stimulates its own synthesis means that taking it does not suppress the body's ability to synthesize it, as happens with cortisol. Sometimes, one dose or a few doses can restore the body's ability to produce enough of its own.

Progesterone also allows the thyroid gland to secrete its hormones, especially when the thyroid function has been inhibited by estrogen. Since the thyroid hormone is needed to produce progesterone, a sup-

plement of either tends to normalize both thyroid and progesterone production.

Progesterone and DHEA are the precursors for the other more specialized steroid hormones, including cortisol, aldosterone (sodium-retaining hormone), estrogen, and testosterone. The formation of these other hormones is tightly regulated, so that taking the precursor will correct a deficiency of a specialized hormone, but will not create an excess. At least in the case of progesterone, an excess tends to balance or neutralize an excess of the specialized hormone, so it has been described as having anti-androgenic, anti-estrogen, anti-aldosterone, and anti-cortisol functions.

Many steroids have a protective ("catatoxic") action against a wide variety of poisons. Some of the quick effects (e.g., within 10 min) of progesterone and pregnenolone probably represent a catatoxic action, as well as a neutralizing or balancing of excessive estrogen or cortisol. Improved metabolic efficiency, sparing oxygen and glucose, will have a quick effect in reducing edema.

During pregnancy, very large amounts of progesterone are made. It protects and stabilizes practically all functions of both the mother and the fetus. Progesterone, glucose and the thyroid hormones powerfully influence the brain development and intelligence of the baby, probably by influencing both the number and the size of brain cells, and the quality of their functioning.

Part of progesterone's protective effect is a result of its quieting effect on cells. For example, it tends to prevent seizure activity in brain cells. During childbirth, its normal function is to act as an anesthetic. When the level of estrogen is too high, progesterone can't achieve this effect. In a non-pregnant person, it is important to determine the minimum effective dose by taking only a few drops at a time, and repeating this small dose about every 20 min until symptoms have been controlled. Otherwise, serious "drunkenness" can be produced, with loss of coordination, and even unconsciousness.

The only solvent for progesterone which isn't toxic and which will dissolve an effective quantity, is vitamin E. In this form, it can be absorbed through the skin or other membranes, or can be taken orally. Taken orally, it is absorbed as chylomicrons, going into the general circulation (as vitamin E does), instead of to the liver where it would be prepared for excretion. In this form, therefore, it is fully and quickly available

to all tissues. It is approximately 20 times more powerful in its action than other preparations, so it is important to use it in physiological quantities, rather than in the huge doses commonly given rectally or by injection. 10 or 20 mg is often an effective dose, though people with low thyroid or high estrogen sometimes use 50 mg/day to 100 mg/day. In the customary 10 % solution, one drop contains about 3 mg progesterone, and 1 mL (1/4 tsp) contains 100 mg The first dose should never be more than 15 mg (An ounce of 10 % progesterone in vitamin E is $15; a dozen one-ounce bottles is $144.)

Pregnenolone, taken orally, does nothing noticeable to a healthy animal or person, but if the stress-related hormones are elevated, they return to normal when pregnenolone is taken. The brain contains much more pregnenolone, DHEA, and progesterone than do other organs or the blood, and these levels decrease progressively with age. Older people are more likely to feel an effect from pregnenolone, than are young people. (A 10 g bottle of pregnenolone is $20; 0.25 kg is $250. 0.1 g is a reasonable first dose, though some people seem to need as much as 1 g/day.)

Thyroid

Measuring the amount of thyroid in the blood isn't a good way to evaluate adequacy of thyroid function, since the response of tissues to the hormone can be suppressed (for example, by unsaturated fats).

In the 1930's accurate diagnosis was made by evaluating a variety of indications, including basal oxygen consumption, serum cholesterol level, pulse rate, temperature, carotenemia, bowel function, and quality of hair and skin. A good estimate can be made using only the temperature and pulse rate.

Oral or armpit temperature, in the morning before getting out of bed, should be around 98 °F, and it should rise to 98.6 °F by mid-morning. This is not valid if you sleep under an electric blanket, or if the weather is hot and humid. A person who is hypothyroid produces heat at a low rate, but doesn't lose it at the normal rate, since there is less sweating, and the skin is relatively cool. Many hypothyroid people compensate with high adrenalin production (sometimes 40 times higher than normal), and this tends to keep the skin cool, especially on the hands, feet, and nose. The high adrenalin is the consequence of low blood glucose, so a

feeding of carbohydrate, such as a glass of orange juice, will sometimes lower the pulse rate momentarily. Healthy populations have an average resting pulse rate of about 85/min. Especially in hot weather it is useful to consider both temperature and pulse rate.

The Achilles tendon reflex is another quick way to estimate thyroid function. This reflex is used because of the insignificant weight of the toes in relation to contraction of the gastrocnemius muscle. The T (repolarization) wave on the electrocardiogram is a similar indicator of the rate of energy production. Thumping the Achilles tendon causes the muscle to contract (unless it is already in a semi-contracted state, which isn't uncommon). The contraction consumes energy, and the muscle can't relax until enough energy has been produced to restore the threshold and the readiness for a new contraction.

If energy production is efficient, relaxation is faster than the passive return motion of the foot, so the foot swings freely back to its original position, and over shoots slightly, causing a slight swinging action. In hypothyroidism, the foot returns as if controlled by a pneumatic door-closer, and settles slowly and precisely into its relaxed position, sometimes with a hesitating, intermittent motion. This slow replenishment of energy, and slow relaxation, can cause muscles to cramp easily. The aching leg muscles of children at the end of an active day are often a sign of hypothyroidism, and sometimes the gastrocnemius muscle becomes very swollen and hypertrophied in hypothyroid children. The same process, of slow energy regeneration, can cause rhythm disturbance in the heart, and often causes insomnia and restless sleep.

The thyroid gland secretes about 3 parts of thyroxin to one part of triiodothyronine, and this allows the liver to regulate thyroid function, by converting more of the T_4 to the active T_3 when there is an abundance of energy. Glucose is essential for the conversion, so during fasting there is a sharp decrease in metabolic rate, and in experiments, 200 or 300 calories of carbohydrates can be added to the diet without causing fat storage.

When the liver is the main cause of hypothyroidism, your temperature (and especially the temperature of your nose, hands and feet) will fall when you are hungry, and will rise when you eat carbohydrates. If a hypothyroid person has a very slow pulse, and feels lethargic, it seems that there is little adrenalin; in this case, a feeding of carbohydrate is

likely to increase both the pulse rate and the temperature, as the liver is permitted to form the active T_3 hormone.

Women often have above-average thyroxin, with symptoms of hypothyroidism. This is apparently because it isn't being converted to the active form (T_3). Before using a Cytomel (T_3) supplement, it might be possible to solve the problem with diet alone. A piece of fruit or a glass of juice or milk between meals, and adequate animal protein (or potato protein) in the diet is sometimes enough to allow the liver to produce the hormone. If Cytomel is used, it is efficient to approximate the physiological rate of T_3 formation, by nibbling one (10 or 25 μg) tablet during the day. When a large amount is taken at one time, the liver is likely to convert much of it to the inactive reverse-T_3 form, in a normal defensive response.

Women normally have less active livers than men do. Estrogen can have a directly toxic effect on the liver, but the normal reason for the difference is probably that temperature and thyroid function strongly influence the liver, and are generally lower in women than in men. Estrogen inhibits the secretion of hormone by the thyroid gland itself, probably by inhibiting the proteolytic enzyme which dissolves the colloid. Progesterone has the opposite effect, promoting the release of the hormones from the gland. At puberty, in pregnancy, and at menopause, the thyroid gland often enlarges, probably as a result of estrogen dominance.

Thyroid function stimulates the liver to inactivate estrogen for secretion, so estrogen dominance can create a vicious circle, in which excess estrogen (or deficient progesterone) blocks thyroid secretion, causing the liver to allow estrogen to accumulate to even higher levels. Progesterone (even one dose, in some causes) can break the cycle. However, if the gland is very big, the person can experience a few months of hyperthyroidism, as the gland returns to normal. It is better to allow the enlarged gland to shrink more slowly by using a thyroid supplement. If an enlarged gland does begin to secrete too much thyroid hormone, it can be controlled with tablets of propylthiouracil, or even with raw cabbage or cabbage juice, and cysteine-rich meats, including liver.

Besides fasting, or chronic protein deficiency, the common causes of hypothyroidism are excessive stress or "aerobic" (i.e., anaerobic) exercise, and diets containing beans, lentils, nuts, unsaturated fats (including carotene), and undercooked broccoli, cauliflower, cabbage, or mustard greens. Many health conscious people become hypothyroid with

a synergistic program of undercooked vegetables, legumes instead of animal proteins, oils instead of butter, carotene instead of vitamin A, and breathless exercise instead of a stimulating life.

Stress and Water

Healing Village E-Zine, August, 2015

THE biological idea of stress refers to the difficulty of adapting, and this involves energy, structure, and insight/orientation. Given enough energy, we can often adjust our structure to achieve full adaptation, and with insight, we can minimize the amount of energy and structural change needed, for example just by a change of pace or rhythm.

Change of structure can involve the growth of new cells, or the enlargement or modification of existing cells, and the shrinking or dissolution (apoptosis) of existing cells, allowing their substance to be used elsewhere. F. Z. Meerson's work gave a clear framework for understanding this, especially in relation to the adapting heart, and Eli Mechnikov's picture of the creative role of the phagocyte in growth can be seen as one of the most basic insights into biology.

A given structure makes possible a certain level of useful energy, and adequate energy makes possible the maintenance of structure, and the advance to a higher and more efficient structural level.

I have been using aging (menopause and the ovaries) and cancer (carbon monoxide as a hormone of "cellular immortality") to explore the issue of cell renewal and tissue regeneration. Yesterday, Lita Lee sent me an article about K. P. Buteyko, describing his approach to the role of carbon dioxide in physiology and medicine. Buteyko devoted his career to showing that sufficient carbon dioxide is important in preventing an exaggerated and maladaptive stress response. He advocated training in "intentional regulation of respiration" (avoiding habitual hyperventilation) to improve oxygenation of the tissues by retaining carbon dioxide. He showed that a deficiency of carbon dioxide (such as can be produced by hyperventilation, or by the presence of lactic acid in the blood) decreases cellular energy (as ATP and creatine phosphate) and interferes with the synthesis of proteins (including antibodies) and other cellular materials.

When I first heard of Buteyko's ideas, I saw the systemic importance of carbon dioxide, but I wasn't much impressed by his idea of intentionally breathing less. If the hyperventilation is produced by anxiety, then a deliberate focussing on respiration can help to quiet the nerves.

Knowing that hyperventilation can make a person faint, because loss of carbon dioxide causes blood vessels in the brain to constrict, I saw that additional carbon dioxide would increase circulation to the brain. This seemed like a neat system for directing the blood supply to the part of the brain that was more active, since that would be the part producing the most carbon dioxide.

In a nutrition class, in the late 70s, I described the way metabolically produced carbon dioxide opens blood vessels in the brain, and mentioned that carbonated water, or "soda water," should improve circulation to the brain when the brain's production of carbon dioxide wasn't adequate. A week later, a student said she had gone home that night and (interpreting soda water as bicarbonate of soda in water) given her stroke-paralyzed mother a glass of water with a spoonful of baking soda in it. Her mother had been hemiplegic for 6 months following a stroke, but 15 minutes after drinking the bicarbonate, the paralysis lifted, and she remained normal.

Later, a man who had stroke-like symptoms when he drank alcohol late at night, found that drinking a glass of carbonated water caused the symptoms to stop within a few minutes.

Realizing that low thyroid people produce little carbon dioxide, it seemed to me that there might be a point at which the circulatory shut-down of unstimulated parts of the brain would become self-sustaining, with less circulation to an area decreasing the CO_2 produced in that area, which would cause further vasoconstriction. Carbon dioxide (breathing in a bag, or drinking carbonated water, or bathing in water with baking soda) followed by thyroid supplementation, would be the appropriate therapy for this type of functional ischemia of the brain.

When there is circulatory stasis, the tendency of the blood to clot is increased. Normally, the legs are where small clots form most often, but the same thing is likely to happen in the brain when circulation is too slow. Carbon monoxide poisoning mimics multiple sclerosis by causing clots to form in the brain, in association with areas of demyelination. Physiologically, I think hypothyroidism, combined with high estrogen (which promotes blood clotting) is the main cause of MS, possibly overlapping with a variety of other demyelinating factors, such as tin, hexachlorophene, heme, and a deficiency of progesterone. One of estrogen's effects is to cause edema, probably because it blocks albumin

synthesis, and the loss of blood volume associated with edema increases the tendency to clot.

People have examined the behavior of carbon dioxide dissolved in water when the water is in contact with the skin, as during a bath in carbonated water. Since the concentration of metabolic carbon dioxide in the living tissue was higher than the concentration in the water, it was assumed that CO_2 would move from the tissue into the water, "down its gradient." But the opposite happened, the carbon dioxide moved from the water into the tissue, against the gradient. This shows that we can draw false conclusions when we think of the body as a "watery system." The carbon dioxide is more soluble in living tissue than in ordinary water, and solubility is what governs the situation, not a context-free concentration gradient. Many natural springs that have a reputation for healing contain carbon dioxide and carbonates, which the body absorbs when bathing in or drinking the water.

Carbon dioxide is more soluble in oil than in water. In general, gases dissolve better in cold water than in warm water, and cold water has more affinity for fats than hot water does. In many ways, the water in cells acts as though it were colder than it is, and more oil-loving. The term "structural temperature" is used to describe the behavior of cellular water which, at body temperature, behaves like ordinary water at a lower temperature–it has a "lower structural temperature." There is a reciprocal action between the cell water and the material it dissolves, so that carbon dioxide tends to stabilize the normal high energy state of the cell. I will say more about cell water after saying a little more about Buteyko's focus on carbon dioxide.

Although it is easy to dismiss Buteyko's emphasis on the "Intentional Cessation of Deep Respiration" as a therapy, his work on the importance of carbon dioxide is sound. When I realized that many hypothyroid people compensate by producing huge amounts of adrenaline, which helps to sustain their blood sugar and their nervous energy, and that adrenaline tends to cause hyperventilation, I saw that "intentional regulation of respiration" might work in these people to reduce hyperventilation just as psychotherapy, reassurance, meditation, or taking a nap can help to control hyperventilation and other effects of excess adrenaline and anxiety. But using carbon dioxide, or a thyroid supplement to promote the body's formation of carbon dioxide, seems like a more logical approach to treatment of a carbon dioxide deficiency.

I have been concerned about the probable effects on the fetus of the silly panting respiration that is being taught to so many pregnant women, to use during labor. Panting blows out so much carbon dioxide that it causes vasoconstriction. Possibly the uterus is protected against this, and possibly the fetus produces enough carbon dioxide that it is protected, but this isn't known. Especially if the mother is hypothyroid, it seems that this could interfere with the delivery of oxygen to the fetus. Besides vasoconstriction, Buteyko points out that the Bohr effect, in which CO_2 causes hemoglobin to release oxygen, means that a low level of carbon dioxide decreases the availability of oxygen. If the Bohr effect applies to fetal hemoglobin, then this suggests that the mother's panting will deprive the fetal tissues of oxygen.

It is normal for the fetus to be exposed to a high concentration of carbon dioxide. Recent experiments with week-old rats show that carbon dioxide, at the very high concentration of 6 % powerfully protects against the brain damage caused by oxygen deprivation (tying a carotid artery and administering 8 % oxygen).[1]

I have talked to several people who get mild neurological symptoms around 2 to 4 AM, and since the symptoms are like those caused by hyperventilation, I think nocturnal low blood sugar and high adrenaline might produce relative hyperventilation and poor oxygenation, possibly with lactic acidemia. A sizable part of the population responds to intravenous lactic acid with a panic attack, and I think these people are hypothyroid ; if glycogen stores are low, lactic acid exacerbates the energy problem, and by displacing carbon dioxide could trigger hyperventilation. When a panic attack is induced by stress, it is probably because the stress is causing the production of lactic acid. Both sugar and carbon dioxide help to prevent panic attacks, according to some recent studies.[2,3]

Buteyko has made an unusual observation, which I think is important. He says that the oxygen deprivation resulting from a deficiency of carbon dioxide can cause increased arterial pressure, and also a dilation of veins, leading to varicose veins and hemorrhoids. (I discussed this behavior of the blood vessels in "A Unifying Principle.") In a lecture, Buteyko argued that a deficiency of carbon dioxide causes allergies, sclerosis, psychosis, tuberculosis, precancerous conditions, and other symptoms.

His list of diseases is reminiscent of Broda Barnes' work, in which he showed that tuberculosis, cancer, and atherosclerotic heart disease are endemic in hypothyroid regions.

This is where the issue of cell water comes in. Carbon dioxide, produced by oxidative cell metabolism, is associated with the high energy state of the cell. When something interferes with oxidative metabolism, lactic acid is produced instead of carbon dioxide. If the cell stays very long in this low oxygen state, it swells, taking up water. (The fatigued muscle, for example, can take up so much water in a short time that it weighs 20 % more than before it began working so intensely that its energy needs far exceeded the availability of oxygen. This swelling is what causes the soreness and tightness of intense exercise. The swelling persists long after the liver has cleared the lactic acid from the blood.)

This swelling from taking up water is involved in one type of "edema," and in inflammation, or activation of the cells by hormones, as well as by simple oxygen deprivation. When the eyes have been closed for several hours, the cornea swells, because it depends on direct contact with the air for its oxygen, and the eyelid, whose circulation provides oxygen for its own cells, doesn't provide enough for the cornea.

Estrogen seems to work by blocking oxidative metabolism, and its first visible effect is to cause the stimulated tissue to take up water.

Anything that causes cells to take up water seems to stimulate cell division. For example, just putting cells in a hypotonic medium stimulates cell division (and a hyperosmotic environment stops cell division).

Years ago I noticed that various enzymes which are activated by estrogen are completely inactivated by cold, and I proposed that estrogen's effect was to raise the "structural temperature" of cell water. If estrogen-stimulated cells have a "high structural temperature," their ability to dissolve oxygen will be reduced. (Whatever the mechanism, estrogen does shift cells away from oxidative metabolism. I think many mechanisms are involved.)

Thyroid, which opposes estrogen's effects on cell energy, stimulates oxidative metabolism with the production of carbon dioxide, and reduces the water content of tissues.

Buteyko suggested that carbon dioxide directly supports immunity. Increasing the availability of oxygen and the production of ATP should be good for immunity, apart from any more specific effects. If it contributes to an effect on the "structural temperature" of cell water, and helps

to raise the energy charge of the cell, CO_2 could be a major factor in opposing the action of estrogen. While the general effects of thyroid can be easily observed, many of its ways of achieving those effects are still not known.

Typical cancer cells are much wetter than normal cells, containing 90 % or 92 % water. It is possible that part of thyroid's anti-cancer, immune promoting effect is the result of the increased carbon dioxide it produces. Since lactic acid turns out to have a variety of "signalling" functions, including effects on white blood cells, it seems possible that carbon dioxide has a different set of signalling or hormone-like functions.

While I doubt that lactic acid produces intracellular acidosis (ATP hydrolysis produces acidosis[4,5]), it can produce temporary extracellular acidosis, besides any specific hormone-like action. This acidosis could be involved in autoimmune processes, since it can change cells' immunological reactivity.[6]

It is very likely that cancer patients lack carbon dioxide, because tumors produce significant amounts of lactic acid, which tends to displace carbon dioxide. It would be interesting to see whether supplemented carbon dioxide would decrease the cancer's production of lactic acid.

Short-chain fats are very soluble, and are quickly metabolized, so it is likely that coconut oil, which is rich in short and medium-chain fatty acids, will tend to decrease the production of lactic acid.

High pressure tends to act as a cell excitant (e.g., it can cause a muscle to contract), and in effect is raising the "structural temperature" of cell water. This suggests that the reduced pressure of high altitude would have the beneficial (antistress) effect of decreasing the structural temperature of cell water. This means that gases would have a higher solubility in cell water at high altitudes, which would tend to slightly offset the biological effect of the relative scarcity of air at high altitude. There is some evidence[7] that reduced pressure increases the solubility of oxygen in cells. The presence of carbon dioxide should increase this effect. (Drost-Hansen discusses some examples of "anomalous" concentration effects of hydrocarbon/water mixtures in "Anomalous Temperature and Pressure Dependencies of Gas Solubilities: Laboratory and Field Observations."[8, p. 254]) I think Drost-Hansen's reasoning suggests that the short-chain fatty acids might also increase the solubility of oxygen in cell water. If this is true, it suggests that coconut oil might

have a very important antistress effect, sustaining efficient respiration during demanding situations.

Some of the other implications of thinking about the special nature of cell water are discussed in the works of Cope[9] and Ling.[10]

Supplement Safety

Townsend Letter for Doctors, May, 1990

AROUND 1976, there were some warnings about the occurrence of kidney and breast cancers from prolonged use of reserpine, which had been very popular for controlling blood pressure. It was thought that the elevation of prolactin by reserpine accounted for the production of tumors. Since tryptophan stimulates prolactin secretions, I thought it might turn out to be just as carcinogenic as reserpine. The people who sell tryptophan don't want to hear this.

Olney's work in the 1970's with aspartic and glutamic acid should have aroused the public to be cautious about the use of isolated amino acids. Even after these amino acids were shown to cause seizures, many companies continued to sell them without warnings.

Orotic acid was known to alter pyrimidine and ammonia metabolism, so I thought it wasn't wise to use supplements that contained large amounts of it. A couple of years ago orotic acid was described as "an excellent liver carcinogen," based on experiments with rats. I have known people who used it regularly in quantities similar to those which are carcinogenic for rats. But it continues to be sold, without warnings.

In 1953, a few small tablets of ascorbic acid completely cured my poison oak and I never got it again though I worked in the woods every summer for several years. But in the late 1950s, I had cold-like symptoms for a few days after I took a 500 mg tablet, and the same thing happened when I took another tablet a few months later. In the late 1960s, I began taking ascorbic acid regularly and I had a chronic cough; about a year later, I developed bleeding colitis. These symptoms stopped when I stopped taking ascorbic acid. I found that I could detect a very small amount of synthetic ascorbic acid in processed foods, by the recurrence of those symptoms. Over the years, seeing other people with similar symptoms, I would tell them about the allergenicity of vitamin tablets or powders, and their symptoms would go away. In this way I saw that the most frequent sensitivity was to ascorbic acid, riboflavin, and rutin. Later, I learned that these are synthesized from cornstarch. Synthetic ascorbic acid contains significant amounts of heavy metals, apparently introduced by the use of sulphuric acid as an oxidant. (The manufacture of sulphuric acid has customarily involved the use of a "lead room." I

don't know whether this technology is still in use.) I experimented with large daily intakes of vitamin C, for example 4000 mg per day in the form of fresh grapefruit juice, and didn't experience any unpleasant reaction, but 1 or 2 mg of the synthetic form—taken by accident in foods such as all-bran breakfast cereal, bread, or sausage, which I didn't suspect would contain added ascorbic acid—would cause days of sickness with intestinal bleeding. Since my reactions to metabisulfite and to synthetic ascorbic acid are similar, though not identical, I suspect that sulfur compounds produced in manufacturing ascorbic acid are partly responsible for its allergenicity.

Interestingly, I have had strong allergic reactions to several kinds of single amino acids; I suspect that these, and many other foods and supplements, are exposed to sulfites or ascorbic acid that have been used as preservatives at some stage of manufacture.

Although more people are writing about the dangers of iron supplementation now than when I wrote about it in *Nutrition for Women* in 1975, it seems that people are using just as much as ever. A hundred years ago, arsenic was the common treatment for "anemia," and it "worked," just as iron works to raise the production of red blood cells. This "anti-anemia" effect is a reaction to injury, and has nothing to do with a nutritional iron deficiency. Even heavy menstruation involves the loss of only 30 or 40 mg of iron per month, or about 1 mg per day, and it is practically impossible to get such a small amount in the diet. Immunosuppression and carcinogenesis by iron have been well established for about 20 years.

Substance Abuse

The Center for Science in the Public Interest got a lot of publicity a few years ago when it petitioned the FDA to require warning labels on products that contain caffeine. Many other groups circulate warnings about the "dangers" of coffee. When coffee was introduced into Europe, some people seemed to think it was an evil witch's brew; Bach's Coffee Cantata ridiculed the great fear of coffee.

To make false claims about anything abuses the truth. A network of mistaken beliefs can lead to a perverted culture, which ignores important issues because of an obsession with false issues. I think it is useful now

and then to outline the kinds of mistakes that are being made regarding the abused substances, coffee and caffeine.

Dr. Minton at Ohio State, and the mass media which mindlessly echoed his beliefs, started a cultish idea that caffeine caused cystic breast disease. His publications are marvels of ignorance and irrationality, which probably someday will be used in college classes to illustrate America's blind faith in the cult of medicine. Other studies found an entire lack of association between caffeine and breast disease, but I will not be surprised if caffeine is ultimately found to be therapeutic for some types of cystic breast disease, because of its effects on hormones and cell-regulation.

Decaffeinated coffee was found to be associated with cancer of the pancreas. A residue of solvent in the coffee is a likely candidate for explaining the association, since the other groups found by epidemiologists to have a high rate of pancreatic cancer were people who work in gasoline stations and in dry-cleaning businesses. Several studies have found caffeine to have a protective effect against cancer. For example, Würzner, et al.[1] found that tumor incidence in rats fed coffee went down as the caffeine content went up.

Caffeine has several effects which protect against cancer. It strongly protects against the cancers caused by chemical carcinogens (including those in smoke), and even against those caused by ultraviolet radiation. It stimulates the repair process which corrects mutations (in mammals, but not in bacteria), and it stimulates the immune system.

I think some of the beneficial effects of caffeine result from its stimulation of the thyroid gland, and of normal respiration. While it stimulates normal respiration it has an anti-inflammatory action, which probably involves both prostaglandin regulation and an antioxidant action. It is chemically very similar to our natural antioxidant, uric acid, and it raises the level of uric acid in both the blood and the urine.

Giving rats the human equivalent dose of 3500 mg/day has no harmful effects, even when continued for several generations. One study found no harmful effects when rats were fed large amounts of caffeine for up to three and a half years. Since lab rats rarely live that long, I think caffeine's effects on longevity should be investigated.

Theophylline, found in tea, is very similar to caffeine. It has been shown experimentally to retard the growth of cancer cells, and even to promote their recovery of normal function. It is widely used to treat

asthma. Theophylline and caffeine have been used to treat apnea in infants, since they stimulate the nerves that regulate breathing. Many people who use theophylline for their asthma don't realize that a few cups of tea would provide the same drug, more pleasantly and less expensively.

Dietitians and their textbooks generally suffer from a cultish belief that coffee and tea "have absolutely no nutritional value." The British found that tea and coffee provide about 20 % of their national dietary intake of several essential nutrients. When the complete absence of certain essential nutrients in white bread was discussed, dietitians defended the use of white bread as an appropriate part of a balanced diet. I mention this simply to establish the cultish nature of their professional behavior, not to advocate the use of whole grains or a larger consumption of tea.

Szent-Györgyi's Energy

Townsend Letter for Doctors, August/September, 1989

A few years ago someone found that yellowing deciduous leaves in the fall were in the state of protein catabolism. I have discussed how this parallels the "toxic" effect of night and winter on animals; the darkness damages mitochondria, and red light seems to be the most effective frequency in restoring their function. The observation that cortisone begins to rise (in humans) when lights are turned out, rather than when people begin to sleep, nicely fits with the rabbit mitochondria studies, and the autumn leaves: either the cortisone causes the damage, or, more probably, the mitochondrial inefficiency wastes glucose, and increased adrenalin, cortisone—and dreaming—are responses to hypoglycemia.

At the moment I am working on the idea that potato plants, which do not normally produce seeds, can be induced to do so by blue (and other high frequency) light—at least when grown in acidic soil which provides iron or other heavy metals which tend to generate free radicals. This idea is a kind of generalization of the idea I first heard around 1953, from an old forester who knew that a coneless pine tree could be caused to produce a heavy crop of seed by injuring it with an ax. There are many other examples of the same process, such as grass which produces seed early when the weather is dry. The many toxic effects of estrogen caused me to interpret its effects (for example, rapid cell division in the uterus) as another example of the same process. In the 1940s, people often talked about famine causing extremely early fertility in girls; although it wasn't much discussed at that time, starvation (and other stress) does cause an elevation of estrogen.

Since Albert Szent-Györgyi died I have been thinking about his idea that the "Hopkins electron pool," stored in cellular proteins provides the energy for cell division. Around 1972, someone reported that sunlight shining on dark hair induces free radicals, and that these free radicals persist for hours in darkness. But exposure to red light "quenches" the free radicals within seconds.[†]

[†] Some people now consider melanin to be an anti-oxidant. It is important not to confuse melanin with lipofuscin, which is produced under oxidative stress and is able to accelerate the wastage of oxygen and energy.

My idea of the "toxicity" of darkness is that free radicals (produced by metabolism, or maybe by cosmic rays) accumulate with time, but that the red component of light normally quenches them. In darkness, the excess of excited electrons would begin to spread beyond their safe storage system, and to cause toxic effects, such as oxygen wastage.[†] Many toxins and stressors are known to act through a common pathway of free-radical damage;[‡] this accounts for the generalized protective effects of certain substances, such as vitamin E (as discussed by Meyerson in *Ray Peat's Newsletter* #29).

One of the most sensitive tests of estrogen's effect is the reduction of a dye (called TTC) by tissue and whole cells;[§] it is reduced (theoretically) by various "dehydrogenases." (The Hopkins electron pool was called by E. Racker "nothing dehydrogenase"). Progesterone blocks estrogen's effects on this dye. Since a similar dye has been used to measure the activity of superoxide dismutase (SOD), it seems that the superoxide radical can reduce the dye. Whatever the source of the electrons, estrogen and progesterone act in different directions on their availability. Progesterone is known to inhibit cell division in various situations: in the uterine endometrium, in cancer, and in frogs' eggs.

Several years ago, someone found that the progesterone in frogs' eggs was bound to the melanin—whose function in the eggs was never

[†] Oxygen wastage itself will block respiration, disrupt mitochondrial function, and allow intracellular calcium to increase. There is clear evidence that many types of cell damage lead to cell death by a common "calcium path." Tissue stress has many self-promoting loops: enzyme release, formation of carbon monoxide and probably cyanide, retention of iron, etc. Sulfur, especially as the sulfane and sulfhydryl forms, is involved in many protective processes: see *Ray Peat's Newsletter* #5, 6 and 50. Deposition of calcium and iron are closely associated, and in oxygen deficiency iron becomes a major source of free-radicals, as discussed in *Newsletter* #41.

[‡] This pathway, according to Meyerson, is closely linked with the calcium-cell-death pathway; supplemental magnesium and vitamin E closely interact in protecting against stress.

[§] Disruption of the cell destroys the ability to reduce the dye, suggesting that something more than ordinary enzymatic reduction is involved. At least, the phenomenon would involve an extreme sensitivity to concentration. This violates the basic assumption of conventional (and stupid) "test-tube biochemistry," namely, that reactions in the test-tube meaningfully reflect what occurs in the cell. Le Chatelier's principle "when a balanced system is disturbed, the equilibrium will shift in a way to restore the original condition," shows how complex enzymes can change activity upon dilution, but this is not generally thought to apply to the dehydrogenases.

understood. (Though Szent-Györgyi for many years emphasized that pigments often exist invisibly inside organisms, and probably have electronic-metabolic functions, rather than the decorative function usually associated with pigments). Melanin generally exists as a complex with proteins. If the energy for cell division is stored in proteins, and if progesterone is acting on the eggs to inhibit cell division, and is bound to the melanin—which is known to store electronic excitation—then maybe progesterone is acting to prevent the escape of energy from the protein-melanin system.[†] If it does this generally, that could explain its very general "catatoxic" effects.

It was around 1954 that I first found some potato fruits, and hoped to get viable seeds with which to grow new strains of potato.[‡] Around that time, John Ott found that squash plants he was photographing with pink artificial light produced only male flowers. The next season he used bluish artificial lights, and his plant produced only female flowers. Later, he found that night blooming plants such as the Morning Glory, could keep blooming if exposed to blue light, but when they were exposed to pinkish light their blooms collapsed.

All of this seems to be converging on the idea that the female reproductive tissues are activated by a free-radical or excited electron promitotic system. But beyond that it seems to have clear implications for aging, stress, toxicity, energy, tissue repair, regeneration, etc. The key idea is that biological structure and biological energy are delicately linked and balanced even at the finest—molecular and submolecular—levels.[§]

[†] In "A Biophysical Approach to Altered Consciousness"[1] I proposed that a "leak" from this system could cause mental symptoms. Substances such as progesterone might have their beneficial psychological and neurological effects by stopping the leak.

[‡] In the winter of 1954–55 I experimented with growing algae under various lights—red, blue, and ultraviolet—to compare with algae grown in daylight, but I didn't have facilities for growing larger plants under those lights, and it has taken more than 30 years to get back to it.

[§] Szent-Györgyi invented this field, called submolecular biology. It shades into Selye's "supra-molecular" biology through the work of many people, such as Gilbert N. Ling, F.Z. Meerson, and Otto Warburg.

Taxol, Yew & Cancer

Townsend Letter for Doctors, February/March, 1992

THE U.S. Government has given a drug company a monopoly on the exploitation of the rare and slow-growing yew tree, to make a "cancer drug." People who question the propriety of this deal hesitate to speak out, because they feel they might be depriving some woman with ovarian cancer of "the chance to live."

We should remember that our cancer establishment, the alliance between government and the medical/pharmaceutical industry, has been claiming victory against cancer for several decades, while the death rate from cancer has steadily increased. This discrepancy between their claims and reality can be understood with the help of three facts:

1. By increasing the number of people diagnosed as having cancer, the "cure" rate can be increased. Every middle-aged person has some tissue that could be diagnosed as "cancerous." Soon, magnetic resonance imaging will be so sensitive that most of those "cancers" can be found, and the "cure rate" will rise to about 90 %, but the death rate from cancer won't decline.

2. The baby-boom that followed World War II caused the rate of increase in cancer mortality to decline, because most cancer occurs in older people, and they were becoming a smaller percentage of the whole population. The same tricks used by the cancer industry could allow someone to claim that the "standard" lifespan was now about 92 years. Although this is statistical fraud of the crudest sort, it has been consistently accepted and promoted by university scientists of the "first rank," who benefit financially from the misrepresentation.

3. The same baby-boom caused an increase in childhood leukemia. At the same time, radiation from atomic bomb testing and prenatal X-rays caused a real increase in the risk of leukemia. The American Cancer Society used 1940 for "age-standardization" to make the general cancer rate look better, but they re-standardized when talking about childhood leukemia, so their calculations would show a downward trend. The downward trend in childhood disease was naturally produced by a declining birthrate, the end of the baby boom, but it was undoubtedly reinforced by the end of atmospheric nuclear testing and by the decreased

use of prenatal X-rays. But these figures are the basis for the cancer industry's main claims of success.

Many poisons can cause tumors to shrink, and the yew tree contains such poisons. But shrinking a tumor has nothing to do with increasing a patient's survival prospect. The quack-busters have made that point many times in attacking "unproven cancer remedies."

At best, taxol is an unproven cancer remedy, but when a drug monopoly is promoting a new product, facts hardly matter.

The mechanism of taxol's cytotoxicity is probably similar to that of colchicine, namely, interference with the microtubule system. Microtubules are essential for cell division and many other cell functions. The goal of cytotoxic chemotherapy is to block cell division in cancer, without destroying cell division in essential tissues such as blood, the intestine's lining, skin, and the immune system. Certain cells of the immune system are uniquely fragile, and this fragility sometimes makes it possible to kill a cancer derived from those fragile cells, without killing the patient. The use of glucocorticoid hormones to destroy thymus-derived cancers takes advantage of that natural sensitivity and fragility.

Besides cell division, many (if not all) cellular functions depend on normal microtubule physiology. Microtubules are especially prominent in nerve cells. They are involved in axonal transport. It is not surprising that taxol is very toxic to nerve cells.[1,2] Microtubules are probably involved in the amoeboid movement of white blood cells, and taxol is very toxic to the neutrophils. Microtubules are involved in the fusion of their digestive enzyme vacuoles with their phagocytic vacuoles.[3] The neutrophils, effective tumor cell killers, would not be poisoned by a rational therapy. (These cells also govern wound healing and tissue remodeling, and I will discuss them later in relation to aging and regeneration.)

The metabolism of cholesterol into pregnenolone and progesterone (which are natural anti-cancer factors) is blocked by taxol.[4] Adrenalin secretion is also inhibited by taxol,[5] and adrenalin too, has some relevance to cancer control, e.g., it is anti-mitotic.

Certain cytotoxic treatments have a very rational basis. For example, cyanide poisoning followed by thiosulfate detoxification, is based on the fact that cancer cells consistently lack the enzymes for detoxifying cyanide by combining it with sulfur. Cyanide is too cheap to warrant serious consideration as a cancer therapy. (The pharmaceutical industry has undoubtedly considered promoting their cancer drugs to replace

cyanide in capital punishment, but so far death by torture is acceptable only for cancer patients.) The established specificity of cyanide/thiosulfate toxicity for cancer cells contrasts with the generalized toxicity of taxol, which could be classed with whole-body irradiation as a desperate and irrational approach.

One aspect of taxol research might advance our understanding of the body's defenses against cancer. It happens that taxol, like bacterial endotoxin, stimulates macrophages to secrete tumor necrosis factor (TNF). This knowledge might lead to an insight into the nature of the process that controls TNF, and how that process fits into normal immunity. Promoting the body's natural immunity, combined with reducing our exposure to cancer-causing factors, should have higher priority in the health sciences, but the power of the drug industry focuses attention on the idea of medically killing cancer cells.

William McGuire (Johns Hopkins School of Medicine) reported in 1989 that 12 patients out of 48 with "refractory" ovarian cancer[6] "responded" to taxol treatment. All but two of the patients were dead by July, 1991. Ninety-six percent mortality doesn't sound very good.

A study at the University of Pennsylvania Cancer Center[7] found that, in patients with extensive malignant disease, there was no difference in survival time for patients who got conventional treatment, and 78 similar patients who were treated with unorthodox methods at the Livingston-Wheeler Clinic. A growing number of physicians recognize the uselessness of most conventional treatments.

A 77 year-old friend of mine had a physical examination, and learned that he had prostate cancer, though there had been no symptoms. As soon as he was given estrogen "therapy," he became miserable, and was never comfortable again, and died of a stroke a few months later. He believed that the misery was "extending" his life, because that is what his physician told him. There is clear evidence that estrogen does not prolong survival in prostate cancer patients, and the often cited "research" which is said to show the efficacy of estrogen treatment was nothing but a survey of doctor's opinions. The survey was done at a time when it was believed that prostate cancer is caused by testosterone, and that estrogen antagonizes testosterone. In fact, animal experiments show that estrogen causes prostate cancer, and *in vitro* tests show that it, but not testosterone, stimulates cell division in human prostate tissue. Progesterone, which antagonizes both estrogen and testosterone, has

been used to shrink enlarged prostates, but estrogen continues to be used to treat prostate cancer.

If poisons are going to be used against cancer, they should be more toxic to the cancer than to the patient, and they should extend the patient's lifespan, and/or decrease suffering.

A very competent cancer researcher found that the patients who delayed longest in going for medical treatment for cancer had the longest survival. If patients would remind their doctors to "first do no harm," there might be fewer lives lost in the heroic "war against cancer."

The Bean Syndrome

Townsend Letter for Doctors, 1993

An extract of the common bean (phytohaemagglutinin, PHA) is widely used in research, and has been used occasionally in medicine. The effects of bean toxin, and other plant toxins (e.g., pokeberry) overlap in several ways with viral infection and autoimmune disease. PHA causes, for example, the appearance of large mononuclear cells in the blood, the suppression of DNA synthesis in thymic cells, a slight leucopenia, and hepatic necrosis. Extracts of lentils, broad beans, and fenugreek (used in curry) are as active as PHA, and extracts of common peas, chick peas, lupinus, and soy beans also have some activity. The effects of a single exposure (such as eating a pokeberry) can remain microscopically visible for two weeks.[1]

In aging, stress, and malnutrition, the barrier function of the intestine is weakened. Vitamin A and magnesium deficiencies allow macromolecules to enter the blood from the intestine.[2]

Injury to the bowel causes"flu-like" symptoms. There have been reports that the viruses of "respiratory diseases" appear in the intestine before they appear in the respiratory tract. Alvarez found that"when a dog gets distemper the gradient of latent period down its small bowel is reversed," and he suggests that in a cold"a systolic, non-progressive type of contraction appears." He says codeine is the best medicine to block a cold. (I have argued that it is vitamin C's laxative action which can interrupt cold symptoms.) Recent research shows that naloxone, the morphine antagonist, can restore normal responses to the stressed bowel. Alvarez was interested in chronic fatigue and"painful fatigue," and remarked that occasionally"a fatigue state will follow a bout with some infection such as influenza."[3]

Bacterial toxins, whether produced in the intestine or in the manufacture of food supplements, pass through the wall of the intestine in larger amounts in stress, malnutrition, and old age. Endotoxin suppresses mitochondrial respiration, and tends to produce a shock-physiology similar to that produced by endogenous hormones. I have mentioned before that I think endotoxin can be involved in the premenstrual syndrome, and I think it might even be involved in some breast syndromes.[4,5]

Two features of mitochondrial damage in severe stress (regardless of whether endotoxin is involved) are a depletion of the antioxidant reserves, and loss of the ability to convert cholesterol into the protective steroid hormones. Mitochondrial damage is more likely in hypothyroidism, as I have discussed previously; thyroxin inhibits lipid peroxidation, end it tends to be inversely related to adrenalin, preventing or minimizing"catecholamine toxicity," for example. Beans and lentils happen to be powerful anti-thyroid agents, so it isn't surprising to see indications of decreased aerobic capacity, resulting from decreased peak oxygen consumption[6] in association with the chronic fatigue syndrome (CFS), if that syndrome is caused by chronic exposure to dietary legumes.

Hypothyroidism causes poor magnesium retention, so the report that a magnesium supplement caused reduced pain and improved energy level and emotional state, while increasing intracellular magnesium in CFS patients,[7] suggests a role for hypothyroidism in CFS. One of the symptoms specific to chronic fatigue syndrome[8]—postexertional malaise, marked by pain and weakness and by an exacerbation of other symptoms including fever and adenopathy—can be explained as the result of increased absorption of bowel toxins which follows the relative ischemia of the intestine during intense adrenergic stimulation.

A day or more after eating an allergen, it can be resting harmlessly in the intestine, and exertion, or emotion, or hunger, or nighttime can lower the blood sugar enough to cause a surge of adrenalin. The adrenalin reduces the flow of blood to the intestine, allowing allergens to be absorbed via the de-energized tissues. If the blood sugar stays low in spite of the adrenalin, white cells will be stimulated to release histamine and other pro-inflammatory substances, but the adrenalin will also cause the secretion of glucocorticoids. Night-sweats and neurological symptoms can be produced by these hormonal responses. The glucocorticoids first induce, then—at high levels—destroy the detoxifying enzymes.

Special conditions, such as a bowel infection, or immaturity of the intestine, can allow large amounts of allergens to pass through the intestinal barriers. In Los Angeles, I learned that physicians and nutritionists often advise welfare mothers to start feeding beans to their babies at six months. In parts of Africa, babies are given"bean milk" from the

beginning instead of milk. The Epstein-Barr virus, which is believed[†] to cause Burkitt's lymphoma and infectious mononucleosis, has often been proposed as a cause of the chronic fatigue syndrome. R. J. V. Pulvertaft[9] found"a close similarity between Burkitt cells and human lymphocytes stimulated by bean extract." He concluded that"...the possibility of a relation between Burkitt's lymphoma and a diet of beans should not be neglected," though he emphasized that other factors must be considered, since most people who eat beans don't develop the disease. The intestinal parasites which are common in tropical Africa can cause inflammation of the bowel, leading to the absorption of large amounts of antigens.

Since the bowel becomes inflamed in influenza, it is reasonable to think that some of the symptoms of"the flu" are produced by absorbed bowel toxins. The variations in the post-influenza syndromes are very likely influenced by the nature of the bacteria or foods which are present, chronically or at the time of an uncompensated stress or inflammatory disease. K. M. Stevens[10] has argued that while rheumatic fever and glomerulonephritis are caused by the antigens of streptocci, systemic lupus erythematosis (SLE) is probably caused by the antigens of gram-positive lactobacilli found in the normal flora.

Migraine, SLE, CFS, thyroid problems, and some kinds of porphyria seem to be more common in women of reproductive age, and are often exacerbated by premenstrual hormone changes. According to Stevens,"SLE is almost entirely a disease of women of child-bearing age. One possibility for this selection could be that women during this period harbour a peculiar flora. This is indeed the case; large numbers of gram-positive lactobacilli are present in the vagina only during the thirty-odd years when regular menstrual activity is present." In 1974, I noticed that I consistently got a migraine headache after drinking a lactobacillus milk product, and stopped using (and recommending) yogurt and other lactobacillus foods, though I suspected it was the lactic acid which caused the symptoms. I still consider lactic acid to be a metabolic burden, especially when combined with an estrogen excess, but Stevens' main point, about the significance of our immunological response to systemic bacterial antigens, deserves more attention.

[†] Antibodies to this virus can be found In 90 % of the population, so it isn't very meaningful to say that it "causes" those particular conditions.

I have previously discussed the use of antibiotics (and/or carrot fiber and/or charcoal) to relieve the premenstrual syndrome, and have mentioned the study in which the lifespan was extended by occasionally adding charcoal to the diet. Recently, I heard about a Mexican farmer who collected his neighbors' runt pigs, and got them to grow normally by adding charcoal to their diet. This probably achieves the same thing as adding antibiotics to their food, which is practiced by pig farmers in the U.S. to promote growth and efficient use of food. Charcoal, besides binding and removing toxins, is also a powerful catalyst for the oxidative destruction of many toxic chemicals. In a sense, it anticipates the action of the protective enzymes of the intestinal wall and the liver.

Our normal defenses against environmental toxins include a surface layer of mucus, the IgA antibodies on membranes, the brush border of intestinal cells, on which protein digestion normally takes place, enzymes in the intestine and liver which hydoxylate and glucuronidate smaller molecules of toxins, and binding-proteins, such as albumin and metallothionein, all of which keep toxins from entering other parts of the body. When toxins get past those barriers, survival depends on other adaptive factors, including the catatoxic steroids and the antioxidative systems.[11,12] Besides metabolizing exogenous toxins, the detoxifying enzymes of the monooxygenase system metabolize endogenous substances, including steroids, prostaglandins, and polyunsaturated fatty acids, which affect allergic reactivity. An imbalance of this system can waste the protective steroids.[13]

Recently, it has been argued that the allergic reaction itself functions as an immunological defense against toxins.[14] However, when the intestine and liver are injured, the production of cholesterol is often decreased to such a great degree that there isn't enough to maintain adequate production of the catatoxic and anti-inflammatory steroids. Many people with the allergic fatigue syndrome have a dangerously Iow blood cholesterol level of 90 mg/dL to 130 mg/dL. (Fruit, because of its fructose content, usually helps restore liver cholesterol synthesis.)

Undercooked and raw plant materials in general are important sources of toxins and allergens. Legumes have recently become more important factors in the U.S. diet, because of a complex shift of ideology about the"healthful" diet, which is often associated with a compulsion to "exercise," and sometimes to use stylish, but toxic, food supplements such as tryptophan, iron, and manganese. Ascorbic acid tablets may be

contaminated with enough iron and/or other catalysts to produce a toxic amount of free hydroxyl radicals.[15] In a vegetarian diet containing very little vitamin A as retinol, carotene can sometimes become toxic, since its conversion to retinol requires vitamin B_{12} and other liver functions that seem to depend on adequate thyroid function, and excessive carotene can be anti-thyroid as well as anti-steroidogenic. A deficiency of retinol can damage the barrier functions or membranes, various immune functions including antibody formation, and the synthesis of protective steroids.

Some women with premenstrual fatigue have found that the"premenstrual" phase tends to get longer and longer, until they have chronic fatigue. I found that to be one of the easiest"PMS" problems to correct. When people are older, and have been sick longer, the fatigue problem is likely to involve more systems of the body. The larger the quantity of"toxic fat" stored in the body, the more careful the person must be about increasing metabolic and physical activity.

Using more vitamin E, short-chain saturated fats, and other anti-lipid-peroxidation agents is important.

Sixty years ago, people with chronic fatigue were often said to suffer from"nervous breakdown," and advised to go to a sanitarium for a vacation, and to stop bothering the doctor. A change of activity, of place, of work, or of associates can sometimes be very therapeutic. Changing the diet can have social and ideological overtones, and can be done more easily while on a vacation trip. But sometimes the problem can be solved simply by avoiding some vegetable materials and food supplements, and/or by correcting hormonal problems, and/or by modifying the intestinal ecology.

The Dire Effects of Estrogen Pollution

NaturoDoc, April, 2006

POLLUTION of the environment and food supply by estrogenic chemicals is getting increased attention. Early in the study of estrogens, it was noticed that soot, containing polycyclic aromatic hydrocarbons, was both estrogenic and carcinogenic. Since then, it has been found that phenolics and chlorinated hydrocarbons are significantly estrogenic, and that many estrogenic herbicides, pesticides, and industrial by-products persist in the environment, causing infertility, deformed reproductive organs, tumors, and other biological defects, including immunodeficiency.

In the Columbia River, a recent study found that about 25 % of the otters and muskrats were anatomically deformed. Estrogenic pollution kills birds, panthers, alligators, old men, young women, fish, seals, babies, and ecosystems. Some of these chemicals are sprayed on forests by the U.S. Department of Agriculture, where they enter lakes, underwater aquifers, rivers, and oceans. Private businesses spray them on farms and orchards, or put them into the air as smoke or vapors, or dump them directly into rivers. Homeowners put them on their lawns and gardens.

Natural estrogens, from human urine, enter the rivers from sewage. Many tons of synthetic and pharmaceutical estrogens, administered to menopausal women in quantities much larger than their bodies ever produced metabolically, are being added to the rivers.

In the same way that weak estrogens in the environment may become hundreds of times more estrogenic by synergistic interactions,[1] combinations of natural, medical, dietary, and environmental estrogens are almost certain to have unexpected results. The concept of a "protective estrogen" is very similar to the idea of "protective mutagens" or "protective carcinogens," though in the case of estrogens, their promoters don't even know what the normal, natural functions of estrogen are.

In November 1995, an international conference was held to study the problem of "environmental endocrine-disrupting chemicals" and devise strategies for increasing public awareness of the seriousness of the problem. Their "Statement from the Work Session" says: "New evidence is especially worrisome, because it underscores the exquisite sensitivity of the developing nervous system to chemical perturbations that result in functional abnormalities."

This work session was convened because of the growing concern that failure to confront the problem could have major economic and societal implications. "We are certain of the following: endocrine-disrupting chemicals can undermine neurological and behavioral development and the subsequent potential of individuals…" Because the endocrine system is sensitive to perturbation, it is a likely target for disturbance.

Man-made endocrine-disrupting chemicals range across all continents and oceans. They are found in native populations from the Arctic to the tropics, and, because of their persistence in the body, they can be passed from generation to generation. Many endocrine-disrupting contaminants, even if less potent than the natural products, are present in living tissue at concentrations millions of times higher than the natural hormones. The developing brain exhibits specific and often narrow windows during which exposure to endocrine disruptors can produce permanent changes in its structure and function.

In spite of this increased exposure to estrogens, there is a new wave of advertising of estrogenic substances, based on the idea that weak estrogens will provide protection against strong estrogens. The environmental background of estrogenic pollution already provides a continuous estrogenic exposure. In the 1940s, Alexander Lipshuts demonstrated that a continuous, weak estrogenic stimulus was immensely effective in producing, first fibromas, then cancer, in one organ after another, and the effect was not limited to the reproductive system.

How is it possible that the idea of "protection" from a weak estrogen seems convincing to so many? Isn't this the same process that we saw when the nuclear industry promoted Luckey's doctrine of "radiation hormesis," literally the claim that "a little radiation is positively good for us"?

DES (diethylstilbestrol) is one of the most notorious estrogens, because studies in humans revealed that its use during pregnancy not only caused cancer, miscarriages, blood clots, etc., in the women who used it but also caused cancer, infertility, and deformities in their children and even in their grandchildren. (But those transgenerational effects are not unique to it.)

Besides the absurd use of DES to prevent miscarriages, around 1950 it was also used to treat vulvovaginitis in little girls, for menstrual irregularity at puberty, to treat sterility, dysfunctional bleeding, endometriosis, amenorrhea, oligomenorrhea, dysmenorrhea, migraine headaches, nau-

sea, and vomiting, and painful breast engorgement or severe bleeding after childbirth.

DES is a "weak" estrogen in the sense that it doesn't compete with natural estrogens for the "estrogen receptors." (Estriol binds more strongly to receptors than DES does.[2]) Pills formerly contained 5 mg to 250 mg of DES. The 1984 PDR lists doses for hypogonadism and ovarian failure as 0.2 mg to 0.5 mg daily. In general, the dosage of estrogens decreased by a factor of 100 after the 1960s.

An aggressively stupid editorial by Alvin H. Follingstad[3] is being circulated to promote the use of estriol, or phytoestrogens. It argues that women who secrete larger amounts of estriol are resistant to cancer.

By some tests, estriol is a "weak estrogen"; by others, it is a powerful estrogen. When estriol was placed in the uterus of a rabbit, only 1.25 μg was sufficient to prevent implantation and destroy the blastocyst.[4] Since the effect was local, the body weight of the animal doesn't make much difference when thinking about the probable effect of a similar local concentration of the hormone on human tissues. The anti-progestational activities of estriol and estradiol are approximately the same.[5]

When 5 mg of estriol was given to women intravaginally, this very large dose suppressed LH within 2 h and suppressed FSH within 5 h. Orally, 8 mg had similar effects on LH and FSH after 30 days and also had an estrogenic effect on the vaginal epithelium. These quick systemic effects of a "weak estrogen" are essentially those of a "strong estrogen," except for the size of the dose.[6]

When administered subcutaneously, estriol induces abortions and stillbirths.[7]

Another indication of the strength of estrogen is its ability to cause the uterus to enlarge. Estriol is slightly weaker, in terms of milligrams required to cause a certain rate of uterine enlargement, than estradiol.[8] But isn't the important question whether or not the weak estrogen imitates all of the effects of estradiol, including carcinogenesis and blood clotting, in addition to any special harmful effects it might have?

When added to long-term cultures of human breast cancer cells, estriol stimulated their growth and overcame the antiestrogenic effects of tamoxifen, even at concentrations hundreds of times lower than that of tamoxifen. "The data do not support an antiestrogenic role for estriol in human breast cancer."[9]

Studies of the urinary output of estriol and estradiol in women with or without breast cancer do not reliably show the claimed association between low estriol and cancer, and the stimulating effect of estriol on the growth of cancer cells suggests that any alteration of the estrogen ratio is likely to be a consequence of the disease rather than a cause. The conversion of estradiol to other estrogens occurs mainly in the liver of the non-pregnant woman, as does the further metabolism of the estrogens into glucuronides and sulfates.

The hormonal conditions leading to and associated with breast cancer all affect the liver and its metabolic systems. The hydroxylating enzymes are also affected by toxins. Hypothyroidism (low T_3), low progesterone, pregnenolone, DHEA, etiocholanolone, and high prolactin, growth hormone, and cortisol are associated with the chronic high estrogen and breast cancer physiologies, and modify the liver's regulatory ability.

The decreased output of hormones when the fetal-placental system is dying is a natural consequence, since the placenta produces hormones and during pregnancy converts estradiol to estriol. Since estradiol in excess kills the fetus, its conversion by the placenta to estriol is in accord with the evidence showing that estriol is the more quickly excreted form.[10] The conversion of 16-hydroxyandrostenedione and 16-hydroxyDHEA into estriol by the placenta[11] would also cause fetal exhaustion or death, resulting in lower estriol production.

But a recent observation that a surge of estriol production precedes the onset of labor and that its premature occurrence can identify women at risk of premature delivery[12] suggests that the estriol surge might reflect the mother's increased production of adrenal androgens during stress. (This would be analogous to the situation in the polycystic ovary syndrome, in which excessive estradiol drives the adrenals to produce androgens.)

Estetrol, which has one more hydroxyl group than estriol, is a "more sensitive and reliable indicator of fetal morbidity than estriol during toxemic pregnancies" because it starts to decrease earlier or decreases more than estriol.[13] This seems to make it even clearer that the decline of estriol is a consequence, not a cause, of fetal sickness or death.

A 1994 publication[14] reported that there are four hormonal features in women with breast cancer: diminished androgen production, luteal

inadequacy, increased 16-hydroxylation of estradiol, and increased prolactin. The 16-hydroxylation converts estradiol into estriol.

A new technique for radiographically locating a hormone-dependent breast cancer is based on the fact that estriol-sulfate is a major metabolite of estradiol. The technique showed the tumor to have about a six-fold higher concentration of estriol-sulfate than liver or muscle.[15]

Another association of elevated conversion of estradiol to estriol with disease was found to occur in men who had a myocardial infarction, compared to controls who hadn't.[16]

The estrogens in clover have been known for several decades to have a contraceptive action in sheep, and other phytoestrogens are known to cause deformities in the genitals, feminization of men, anatomical changes in the brain, as well as functional masculinization of the female brain.[17–20] The effects of the phytoestrogens are very complex because they modify the sensitivity of cells to natural estrogens and also modify the metabolism of estrogens, with the result that the effects on a given tissue can be either pro-estrogenic or anti-estrogenic.

For example, the flavonoids naringenin, quercetin, and kaempherol (kaempherol is an antioxidant, a phytoestrogen, and a mutagen) modify the metabolism of estradiol, causing increased bioavailability of both estrone and estradiol.[21]

Why do plants make phytoestrogens? There is some information indicating that these compounds evolved to regulate the plants' interactions with other organisms—to attract bacteria, or to repel insects, for example, rather than just as pigment-forming materials.[22] The fact that some of them bind to our "estrogen receptors" is probably misleading because of their many other effects, including inhibiting enzyme functions involved in the regulation of steroids and prostaglandins. Their biochemistry in animals is much more complicated than that of natural estrogens, which is itself so complicated that we can only guess what the consequences might be when we change the concentration and ratio of substances in that complex system.

These "natural" effects in sheep were forerunners of the observed estrogenic effects in wild animals, caused by pollutants. Twenty-five years ago I reviewed many of the issues of estrogen's toxicity and the ubiquity of estrogenic substances, and since then I have regularly spoken about it, but I haven't concentrated much attention on the phytoestrogens because we can usually just choose foods that are relatively free of them.

They are so often associated with other food toxins—antithyroid factors, inhibitors of digestive enzymes, immunosuppressants, etc.—that the avoidance of certain foods is desirable.

Recently, an advocate of soybeans said, "If they inhibit the thyroid, why isn't there an epidemic of hypothyroidism in Asia?" I happened to hear this right after seeing newspaper articles about China's problem with 100,000,000 cretins. Yes, Asia has endemic hypothyroidism, and beans are widely associated with hypothyroidism.

When I first heard about clover-induced miscarriages in sheep, I began reading about the subject because it was relevant to the work I was doing at that time on reproductive aging. Sheep, which are adapted to living at high altitudes, where all animals have reduced fertility, have an adaptive type of hemoglobin with a greater affinity for oxygen. Fetal hemoglobin, in animals at sea level, has a great affinity for oxygen, making it possible for the fetus to get enough oxygen, despite its insulation from the mother's direct blood supply. The high-altitude-tolerant sheep have hemoglobin, which is able to deliver sufficient oxygen to the uterus to meet the needs of the embryo or fetus, even during relative oxygen deprivation. These sheep are able to sustain pregnancy while grazing on clover. It seemed evident that estrogen and high altitude had something in common, namely, oxygen deprivation, and it also seemed evident that these sheep provided the explanation for estrogen's abortifacient effects.

Estrogen's effects, ranging from shock to cancer, all seem to relate to an interference with the use of oxygen. Different estrogens have different affinities for various tissues, and a given substance is likely to have effects other than estrogenicity, and the presence of other substances will modify the way a tissue responds, but the stressful shift away from oxidative energy production is the factor that all estrogens have in common. Otherwise, how could suffocation and X-irradiation have estrogenic effects?

Pharmaceutical misrepresentations regarding the estrogens rank, in terms of human consequences, with the radiation damage from fallout from bomb tests and reactor leaks, with industrial pollution, with degradation of the food supply—with genocide, in fact.

Advertising gets a bad name when it can't be distinguished from mass murder. At a certain point, we can't afford to waste our time making subtle distinctions between ignorance and malice. If we begin pointing out the lethal consequences of "stupid" or "quasi-stupid" commercial

or governmental policies, the offenders will have the burden of proving that their actions are the result of irresponsible ignorance rather than criminal duplicity. From the tobacco senators to the chemical, pharmaceutical, food, and energy industries and their agents in governmental agencies, those who do great harm must be held responsible.

The idea of corporate welfare, in which public funds are given as massive subsidies to rich corporations, is now generally recognized. Next, we have to increase our consciousness of corporate responsibility and recognize that ordinary criminal law, especially RICO, can be directly applied to corporations. It remains to be seen whether a government can be made to stop giving public funds to corporations, and instead, to begin enforcing the law against them—and against those in the agencies who participated in their crimes.

In the U.S., the death penalty is sometimes reserved for "aggravated homicide." If those who kill hundreds of thousands for the sake of billions of dollars in profits are not committing aggravated homicide, then it must be that no law written in the English language can be objectively interpreted, and the legal system is an Alice-in-Wonderland convenience for the corporate state.

Notes

As a result of industrial promotion, including product advertising and grants for research, "weak estrogens" and "antioxidants" derived from soy are being discussed as means to prevent breast and prostate cancer, heart disease, stress, and aging. Another so-called weak estrogen, estriol, is being promoted by drug companies for the "alternative medical" market, with the circulation of an editorial from *JAMA* recommending it for preventing breast cancer.

Japanese women used to be very free of breast cancer, and when their children grew up in the U.S., their incidence of the disease was like that of Americans. How odd that the soybean should be singled out for responsibility. Japanese breast cancer incidence has risen sharply in recent years. Did they stop eating tofu? Did their traditional use of seaweed as food have nothing to do with their health? Did the traditional home-bound isolation of Japanese women, their avoidance of smoking and drinking, have no effect on hormones and cancer? Their calorie

intake? Iodine and trace minerals? What types of protein and fat, and in what quantities, did they use?

The Edema of Stress

Townsend Letter for Doctors, May, 1989

OUR medical culture is bloated with retained errors—especially in connection with tissue water and its regulation. Sometimes, just by finding and eliminating errors, a new pattern will reveal itself in the remaining data.

A popular laboratory assignment for students in physiology is to drink a liter of ordinary or distilled water, and to measure the urine output in the next few hours. Then, in the next class (or with different students), a liter of water with 9 g of sodium chloride is drunk. The urine output over the next several hours is about a liter less than in the first experiment. Thus, "sodium causes water retention."

Textbooks base everything on this simple idea that "water follows sodium." "There are," they say, "no water pumps, only sodium pumps in cells."

Two real-world observations reveal the nature of the mistake in that doctrine.

People who work hard in the summer have noticed that their sweat can be so salty that it leaves salty crystals on their hair, and burns their eyes. They may need salt tablets during the day to keep from fainting. But other people, on a low salt diet, can sweat copiously without losing much salt. The body obviously adjusts its salt retention to compensate for salt intake.

By experiment, this adjustment takes only a couple of days. If physiology labs extended their experiments, they would find that sodium does not cause water retention in any sense that matters physiologically. In fact, in both animal and human studies, there are situations in which increased sodium helps to unload excess tissue water.[1,2]

The second real-world observation is that millions of women (in my direct observation, several hundred) have severely restricted their salt intake, yet continue to suffer from cyclic edema. Because of the assumption that "water follows sodium," and that body fluids are "isotonic" (with "isotonic" salt solutions, or with intracellular fluids), people seldom measure the osmolarity of blood plasma or serum. Estrogen causes the retention of water independently of sodium, causing the

molarity of the plasma to decrease. Uremia and, in general, old age cause the molarity of the blood to increase.

Seeing that salt restriction never helped women with cyclic edema, I explained the mechanisms of water regulation, first to just one woman. Within a month, she was salting her food to taste (i.e., salting it heavily in the premenstrual week), and having no trouble with edema. Since then (1978) I have explained this to many women, and it always works for estrogen-induced cyclic edema, and also for the edema of pregnancy induced by excess estrogen,[3] and for the occasional older person for whom it seems appropriate.

Serum albumin with its associated sodium ions, exerts a colloid osmotic pressure which is important in holding water inside blood vessels. Without its associated sodium ions, its intravascular effect is weakened, while the sodium-deficient water tends to cause cellular swelling.

Swelling of tissue cells is the kind of edema which is a serious problem in brain injury and stroke,[4] as well as in traumatic or toxic injury to other tissues, and whenever there is an inadequate supply of energy to cells,[5] as in hypoxia. At a certain point, the resulting pressure of swollen cells outside capillaries can no longer be compensated by adjustments in the blood vessels and increased blood pressure, with the result that tissue perfusion, nutrition and oxygenation are insufficient. (Thus, a severe sodium deficiency contributes to cellular hypoxia.)

When cells can't maintain their energy, they swell if exposed to a standard osmotic environment. This is the ordinary "edema of hypoxia," which is similar to the swelling of cells in tissue culture in "normal isotonic medium."

The conventional story to explain this swelling of hypoxia is that the "sodium pump" requires energy to keep the sodium out, and that inadequate energy allows water to "follow the sodium" into the cell. This explanation is wrong and misleading. While energy deficiency causes cells to swell abnormally, water is also retained by normal cells under the influence of energy. Much of the cell's energy, in the form of protein-bound ATP, regulates the colloidal nature of the cell, including its water content.[6] In this well-tested view of the cell, it would be appropriate to say that "sodium follows water," to contrast its medical implications to those of the "sodium pump" theory, and to create an image of the potentially protective function of sodium.

The generalized edema of hypoxia is closely related to the focal edema which occurs in inflammations and cancers.[7] In a focus of inflammation, the local metabolism, especially of glucose, increases to compensate for a loss of energy. (In a cancer cell, glucose consumption is often several times higher than that of a muscle cell in maximal activity). The focus becomes acidic. The provoking stimulus causes the ATP-protein complexes to break down, with production of ADP and phosphoric acid, and with changes in protein conformation. The increased dispersion of colloids, and the concentration of metabolites such as lactic acid, ammonia, ADP and phosphate, increase the osmotic and oncotic pressure of the cells. The osmotic pressure can be twice normal.

As early as 1920, there were studies of the extremely high osmotic pressure of serum from uremic patients. If there is systemic hypoxia, this very high osmotic pressure of the blood can be seen as a lucky—or adaptive—defense against the tendency of tissues to swell. Circulation can be maintained under conditions which otherwise would cause tissue swelling and compression of capillaries. Urea is used as a "diuretic" to treat edema of the brain in some circumstances, but it should probably be used more often. A small amount of DMSO (e.g., 1.5%) similarly causes cells to shrink.[8] This would seem to explain much of its anti-inflammatory action (yet the doctrine of "membrane pumps" says that permeant solutes shouldn't cause cell shrinkage). The use of hypertonic urea[9,10] or DMSO, or glucose (about 400 mg/dL, for example[11]) to treat cancer would help to restore circulation, prevent the adaptive leakage of proteins from cells, and allow normal regulatory processes to function more efficiently.

Serum albumin is one of the body's most powerful tools in maintaining homeostasis. Gilbert Ling has demonstrated that serum albumin or collagen, when "denatured" by urea, has a greatly increased oncotic pressure, or tendency to retain water.[12] Under physiological conditions, it is probably a variety of solutes, especially free fatty acids, which cause albumin to adjust its oncotic pressure.

I think the extremely quick changes that sometimes occur in extracellular connective tissue substance (e.g., in arthritis, exophthalmia, or glaucoma) in response to progesterone, pregnenolone, DHEA, or other related steroids, are likely to result from a similar physical effect on the colloidal osmotic pressure of the body fluids, and possibly of the

connective tissue substances themselves. Diffusion of oxygen through the lungs can be obstructed by layers of colloidal material, and steroids are involved in mitochondrial structure and stability and other cellular processes, so I don't mean to deny that these hormones also have other powerful effects, just that some early effects in relatively inert tissues are so quick that shifts in water content seem to be the best explanation.

Knowing that old organisms are relatively dehydrated, it is interesting to see that when a young muscle is made to lose some of its water, it functions similarly to a muscle from an old animal.[13] Recently, enzymes from old animals were denatured, causing them to lose their specific folded arrangement. When they were carefully "renatured," it was found that their enzymic function had increased, to become the same as that of enzymes from young animals. This shows that the nature of the "solution" in the cell, the conditions under which the enzymes are synthesized, has subtly modified their shape. Restoring the cell's energy, which governs the cell's colloidal state, might be able to restore all cellular functions to the active, young state, though this state would have to be maintained until protein "turnover" had renewed a large part of the cell structure. ("Protein turnover" refers to the normal process of renewal, in which some proteins are destroyed while new ones are being made).

Energy, in the form of ATP with magnesium, can be effectively supplied to tissues through the blood stream.[14–16] (Again, it has been the dogma of the "semi-permeable cell membrane" which has blocked the acceptance of this work: ATP simply couldn't get into cells, they said).

Energy, produced under the influence of the thyroid hormone (triiodothyronine, T_3), and acting to eliminate edema, can correct many problems that don't seem to have anything to do with "energy." The carpal tunnel syndrome, involving swelling in or around nerves, is often relieved by a thyroid supplement, or by avoiding anti-thyroid foods such as beans and seed oils. (Surgery to relieve the pressure caused by swelling is the conventional treatment).

Several people with a diagnosis of "multiple sclerosis" recovered immediately and fully when given thyroid. (Triiodothyronine does influence myelination,[17] but I think the important causal sequence is: first, disturbed respiration, then edema, then demyelination).

Many animal diseases, produced by copper deficiency and its associated respiratory defect, involve swelling of the brain and/or spinal cord.

Dogs, horses, and sheep develop weakness or paralysis of the hind legs, as a result of compression of the edematous spinal cord. In chronic copper deficiency, cells absorb an excess of iron,[18] so treatment isn't just a simple matter of giving supplementary copper.

Hyperoosmotic therapy, to directly relieve the swelling and restore circulation, would probably have to be the first step. In treating either hypoxia or iron-overload, there is the danger of tissue injury from the free radicals produced by reduced iron.

There are many practical, simple consequences of recognizing the interactions of osmotic pressure, metabolism, and inflammation. For example, people with inflammation of the bowel, resulting in obstruction that can't be relieved by an ordinary enema, have found that a hyperosmotic enema (sometimes with aspirin added) can relieve the edema which is causing the obstruction.

The Generality of Adaptogens

Townsend Letter for Doctors, 1991

THERE are far more sensory nerves entering the brain, than motor nerves leaving the brain. Generalization and judgment intervene between the complexity of sensation and the coherence of behavior. Encountering an infinite world, we marshall our resources for an adequate response. For me, this "sensory domination" of the brain is an important metaphor that offers some insight into other systems, because it suggests that interesting events of integration might be happening "above" the easily observable mechanical behavior of a particular system that we are trying to understand.

To bring generality to the understanding of cellular resistance, we should look for events that commonly occur during successful or unsuccessful responses to stressors of various types. Several years ago, someone found that a "final common pathway" of cellular death was the absorption by the cell of a large amount of calcium, when the cells were injured in a variety of ways. Working with the stressed heart, F. Z. Meerson spoke of the "calcium triad," suggesting that there are ways to interrupt the progress of cellular death even after it has started. Calcium activates proteinases, phospholipasis, ATP-ases, contraction and oxidative peroxidation, and uncouples oxidative phosphorylation, so that numerous drugs can interfere with various aspects of the cellular death process after it has begun. Knowing that calcium is a normal activator of muscle contraction and other normal processes, we can consider the normal physiological controls over calcium, as places where a little extra support might keep our cells safely away from the "final common pathway" of cell death.

In different situations, we can see different components of a "terminal" process. For example, iron tends to accumulate with age, and areas of calcification in soft tissue typically show iron associated with the calcium. (This association is probably both physicochemical and pathophysiological.) Vitamin E is protective against the lipid peroxidation induced by iron,[1] as well as that stimulated by calcium. Mice killed by a variety of methods show a high level of histamine in their tissues, suggesting that histamine might be involved in a "terminal pathway" on either the organismic or the cellular level. Histamine can stimulate the

entry of calcium into cells.[2] On the organismic level there are hormonal changes that accelerate the progress into a terminal state, and several of these are closely associated with the metabolism of calcium (cortisol, prolactin, and estrogen). Others are associated with the suppression of thyroid function.

Adaptogens are chemicals which increase an organism's ability to resist stress without suffering cumulative damage. This is a useful definition, since it excludes the glucocorticoids, which promote adaptation and short term resistance to stress, but do so at the expense of the organism's future reserves. Every aspect of our normal resistance that precedes our resort to cortisol can suggest possible classes of adaptogenic substances to strengthen those functions. The avoidance, binding, and detoxifying functions are all part of adaptation, but the most important aspect of adaptation is the ability to maintain a high level of tissue energy, and the stabilization of respiratory energy production is needed for that. Besides the oxidative production of energy, we need to prevent the wasteful expenditure of energy, and this requires the ability to raise thresholds to stimulation. (We can see both of these processes working in the adaptation of a healthy child to a serious infection: having a fever, and sleeping.)

As soon as something interferes with the oxidative production of energy (not having enough oxygen, for example, as when running) we adapt biochemically first by increasing the consumption of glucose for glycolytic energy production. This increased consumption of glucose tends to lower the concentration of glucose in the blood, and this (or various other signals, such as pain or fear, that are associated with the need for more glucose) causes the secretion of adrenalin, which can mobilize glucose from the liver's glycogen stores. If the glucose stores are depleted, the body resorts to the secretion of cortisol, to provide glucose (and other material) by cannibalizing protein from tissues which are momentarily less essential.

Both adrenalin and ACTH mobilize fat from storage. Stress-mobilized fatty acids contribute to the increased lipid-peroxidation seen during stress, and they also tend to damage mitochondria. The large increase in the death rate from asthma in the last decade or two is

now believed[†] to be the result of cardiovascular damage caused by the common use of inhalants containing catecholamines. Isoproteron01, a commonly used bronchodilator, causes mitochondrial damage, which can be prevented by blocking the carnitine-dependent oxidation of fatty acids. Since carnitine is required for the oxidation of long-chain fatty acids, its analog-betaines (which interfere with its transport of fatty acids into the mitochondria) protect against the damage that normally results from stress-induced (or catecholamine-induced) fatty acid oxidation. Since saturated fats protect against the cardiac necrosis produced by corn oil, I think it is probably lipid-peroxidation resulting from rapid oxidation of unsaturated fats which causes the heart damage in both catecholamine damage[3] and corn-oil toxicity. Vitamin E, coconut oil, and the carnitine antagonists (betaine derivatives) are adaptogens that protect respiration by directly decreasing lipid-peroxidation.

Uncompensated stress or injury is a complex process, so it shouldn't be suprising that adaptogens have a "broad spectrum" of beneficial biological effects, but it is precisely the breadth of vitamin E's effect that have made many physicians reluctant to use it, because they are trained to think in terms of "lock and key" specificity in pharmacology. The same reaction can be expected from drug-dominated medicine, as results with other adaptogens are published. For example, a Soviet adaptogen of the betaine class which is used as a feed-additive for animals, has been reported:

- induce interferon and protect against influenza virus,
- protect the brain against hypoxia,
- promote healing of wounds, burns, and sores,
- activate immune responses,
- promote cell division in thymus and spleen,
- restore contractility to hypoxic heart tissue,
- increase the contractile capacity of the heart by increasing ATP concentration,
- prevent decrease of ATP levels under various conditions,
- reduce isoproteronol or catecholamine-induced myocardial injury,
- protect the heart against fatty diets,

[†] Of course, the now discontinued use of sulfite preservative (approved and required by the FDA) in asthma drugs contributed to that high mortality.

- promote methylation of chromatin proteins,
- promote reparative and replicative DNA synthesis,
- increase translation of nucleic acids (protein synthesis),
- stimulate the rate of growth in chickens,
- have very low toxicity, and
- be suitable for use in treating a wide variety of cardiovascular diseases, such as cardiac insufficiency, myocarditis, cardiosclerosis, ischemic heart disease, and arrhythmias of varying etiology, and to have long-lasting positive inotropic effect, and cardiac-dilating activity.[†]

Since the substance seems to be a natural plant growth regulator, and to be cheap to produce, it is probably going to meet serious resistance from the drug industry/FDA monopolists, though the meat industry is likely to eventually find that it replaces many of the toxic chemicals that are now used.

The adaptogens of Eleutherococcus and ginseng are already in wide use. It is assumed that their steroidal components support the functions of our own protective steroids. These functions (normally adequately sustained by our endogenous steroids) are probably catatoxic, anticatabolic, anti-inflammatory, and osmoregulatory. Since there is so much talk about catabolic or anabolic steroids, it's important to say something about the anti-catabolic aspect of the protective or adaptogenic steroids.

On a time scale longer than that of the immediate stress experience, preventing cumulative damage is just as important as blocking the immediate injury process. Since cortisol, which is life-saving on the short time scale, is a major cause of cumulative damage to the organism, it is important to investigate things which will limit its chronic catabolic effect.

Although testosterone is very catabolic for the thymus gland, it is anabolic for muscle, and there is some evidence that it is directly competitive with cortisol, which is catabolic for muscle. When radioactive testosterone was injected into a person, the experimenters were surprised to find that its main concentration was in the heart muscle, rather than in the skeletal muscle. This high concentration of testosterone in the heart muscle suggests that an antagonistic relationship between testosterone

[†] Literature search by P. Hockstaff.

and cortisol is responsible for the ability of the heart to retain its protein while starvation or stress is causing protein to be removed from skin muscle, thymus, and other tissues, under cortisol's influence. Such an "anti-catabolic" effect must be especially important during the years of growth, so the youth-associated steroids (prenenolone, progesterone, DHEA) probably serve in this way, while being available for conversion into the more specific hormones. Plant steroids such as those in ginseng, having some structural similarity to the normal protective hormones, would serve as adaptogens by making up for a reduced amount of those normal youth-associated substances.

Filatov found that stressed tissues of both plants and animals produce protective and stimulating substances, which can be extracted for medical use. He identified succinic acid as a component of his extracts. Szent-Györgyi found that succinic acid stimulates respiration, which might explain why it promotes synthesis of pregnenolone and related steroids. It and fumaric acid are now considered to be adaptogens. Since succinic acid safely chelates toxic heavy metals out of mitochondria, it might also safely carry copper into the mitochondria. Succinic acid is also closely associated with GABA metabolism (gamma-amino butyric acid is converted to succinic semialdehyde in a transamination reaction), and so is probably complementary to the GABA analogs GHB (gamma-hydroxy butyrate) and its lactone (which has anti-viral activity). GABA analogs are now one of the most actively studied classes of adaptogens. GABA has a wide range of stress-blocking actions, including neural inhibition, progesterone promotion, and blood sugar regulation.

The "local anesthetics," which generally have a broad range of effects, are an important class of adaptogens. Procaine has been found to normalize almost every system studied.[†] Doses far too small to have an anesthetic effect have clear biological effects. Lidocaine is used to prevent heart arrhythmia, and acts partly by preventing excessive calcium uptake by the cells. The atropine family of drugs is structurally similar to the "local anesthetics," and also have a long history of use in treating sickness and stress. Most of these chemicals have anti-histamine actions that are probably relevant to their value as adaptogens. These chemicals can protect microcirculation against spasms produced by exhaustion or overstimulation. Light can also have this effect.[4]

[†] One large study was done at Edgemoor Geriatric Hospital, Santee, California, in 1960.

Promotion of synthesis and stabilization of the detoxifying enzymes is another function of some adaptogens. The catatoxic steroids do this, but since they also have an immediate protective effect (that could hardly involve the production of new enzymes), they probably have other mechanisms of action, such as improving the capacity for binding toxins of proteins such as albumin. Since even cholesterol has catatoxic action, I often advise people to eat more eggs for a variety of problems. The egg lipids (including phospholipids and cholesterol) enter the blood in microscopic particles, called chylomicrons. Synthetic "liposomes" are a pharmaceutical fad, promoted for their ability to transport various drugs, but the liposomes themselves (made from egg phosphatidylcholine and cholesterol) have anti-inflammatory and anti-bacterial actions. ("Anti-inflammatory action of liposomes,"[5]) I think we have to include dietary eggs in our list of adaptogens.

I have often described the thyroid hormone as the basic anti-stress hormone, because it is essential for respiratory energy production.[6] The ATP produced under the influence of the thyroid hormone binds magnesium, and is relatively stable in its presence. ADP, the lower energy phosphate that results when ATP loses one phosphate group, happens to bind calcium. Thus, the high energy state of the cell binds magnesium (when it is available), and the low energy state binds calcium. Many of the events that are said to involve "ion pumps" are just different "ion-binding states" of the cell. Both thyroid (to form ATP) and magnesium (to stabilize ATP) are essential for cellular resistance to stress.

Magnesium-ATP, and liposomal-ATP administered intravenously have been used successfully to treat shock and to restore mitochondrial function, and are undoubtedly powerful "adaptogens," but it is much more practical to ingest eggs, magnesium-rich foods, and a little thyroid, to get "cholesterol-liposomes" and magnesium-ATP. Creatine phosphate, which is normally an intracellular energy reserve in balance with ATP, has been found to prevent the heart damage caused by catecholamines.[3] Energy depletion (ATP and creatine phosphate) is probably the central event which precipitates the entry of excess calcium into the cell.[7]

Since many of the biochemical changes in aging are the same as those occurring in stress, the adaptogens tend to relieve the symptoms of aging. And to some extent, relieving the symptoms of aging tends to resist the forces that would otherwise push cells toward the "final common pathways." But the perfect adaptogen would be something

that systematically blocked the agents of damage before any damage had been done. The avoidance of toxins and other stressors (including darkness) should be taken care of before too much emphasis is put on the use of adaptogens. Substances that have one clearly defined adaptogenic function often turn out to have several useful functions. Caffeine, for example, promotes thyroid function, blocks both radiation and chemical carcinogenesis, and inhibits absorption of iron, which under stress has important dysadaptive function.

Filatov's approach, using complex extracts of stressed tissue, suggests that certain methods of food storage and preparation might increase their adaptogen content, e.g., broccoli stored in a refrigerator has much more vitamin C than fresh broccoli; cold-dark storage was one of the stressors Filatov used. The same principle might apply to the use of crude plant or animal drugs. Traditional foods used for convalescents might also include some empirical adaptogens—broths, egg-nog, fruit juice, custards, etc.

Thyroid: Misconceptions

Townsend Letter for Doctors, November, 1993

WHEN I describe some of the simple ways the thyroid gland works, I know that I'm not answering the questions most people have. In the last 50 years, a culture, a mythology, related to thyroid hormone has been manufactured in this country. Now and then, people send me *JAMA*'s latest contribution to that culture. The articles and advertisements in medical journals, and the more direct contacts between drug companies and physicians, have covered most aspects of thyroid physiology with a thick layer of misinformation. A very different story is found in journals of endocrinology, biochemistry, nutrition and metabolism, and in foreign books and journals.

Most of the misinformation is based on something true. If a similar preoccupation with possible harmful side-effects surrounded the rest of medicine as it does thyroid supplementation, medicine would disappear; if it surrounded dietetics, people would starve.

It is sometimes true that "if you take thyroid it will suppress your own gland." By overdosing people until the output of their own glands had gone to zero, it was possible to see what happened when the overdose stopped. Everyone's gland was functioning perfectly again within two or three days. Occasionally, a person whose pituitary isn't producing TSH will respond to thyroid supplementation with normalization of TSH and restoration of their own thyroid gland's function.

It is sometimes (but rarely) true that a person will seem healthy when his serum thyroxine level is near one of the extremes of the "normal" range (which is often given as between 4 or 4.5 μg/dL, and 12 or 14 μg/dL). The story behind that extreme range (imagine a similar "normal" variation for cholesterol, or sodium, or potassium, or anything biochemically important) has to do with a revision in the 1940s of the definition of "normal" to include 95 % of the population, based on the PBI measurement, which was later found to be irrelevant to thyroid functioning.

Thyroxine is often called "the thyroid hormone," in the same way that estrogen has been called "the female hormone." Progesterone is quantitatively and functionally the most important female hormone, and triiodothyronine, or liothyronine, is functionally the most important

thyroid hormone. It is the metabolically active derivative of thyroxine, somewhat as insulin is the activated form of proinsulin. When thyroxine is added to brain tissue *in vitro*, it suppresses respiration; but when triiodothyronine is added to any tissue, respiration is increased. Triiodothyronine (T_3) is mostly produced in the liver, depending on the availability of glucose to the liver, allowing a sensitive adjustment of metabolism to nutrition.

Armour thyroid, USP, is often said to be of imprecise dosage, but in fact every batch is biologically standardized, and studies have shown it to be reliably within 1 % of the labeled potency. The best known brand of the supposedly chemically precise levothyroxine, however, was for a long time 30 % below the labeled potency.

If the liver is the main source of the thyroid problem, then thyroxine pills can make the problem worse, by suppressing the portion of T_3 still coming from the thyroid gland. Armour thyroid, USP, Thyrolar, Euthroid, Proloid, and a few other products contain both thyroxine and T_3, in approximately the proportion secreted by a normally functioning gland.

Unsaturated oils interfere with thyroid function in several ways, including blocking the "digestive" proteolytic enzymes involved in the release of hormone from the globulin. Unsaturated fatty acids interfere with binding of the hormone to a transport protein, and with the conversion of T_4 to T_3 in the liver and in the pituitary. Linoleic and linolenic acids are roughly twice as toxic to these systems as oleic acid is. The tissue response to the hormone is inhibited by unsaturated fats in proportion to the number of double bonds in the fat. A deficiency of polyunsaturated fatty acids is anti-estrogenic, partly by allowing the thyroid-stimulated liver to excrete estrogen, and partly by failing to activate the pituitary secretion of gonadotrophins.

G. W. Crile found that the basal metabolism of the people in Yucatan, where coconuts are a staple food, is 125 % of that of people in the United States. Animal experiments show that coconut oil added to a normal diet can lower serum cholesterol levels. There is a very reliable inverse relationship between the level of serum cholesterol and thyroid hormone action. A major effect of thyroid is to control the conversion of cholesterol into steroid hormones and bile acids.

Thyroid promotes the formation of progesterone, which in turn promotes the secretion of thyroid hormones. Estrogen blocks their release from the thyroid gland, causing the gland to enlarge.

Iodine deficiency used to cause goiters in the United States, but now it is almost impossible to have an iodine deficiency in this country. Iodine supplements can suppress the formation of thyroid hormone, producing classical signs of hypothyroidism.

Hashimoto's thyroiditis is often diagnosed, without appropriate evidence. Even when correctly diagnosed, the knowledge isn't relevant to treatment. Thyroid cells contain estrogen "receptors," and estrogen inhibits thyroid secretion, and excess estrogen is involved in most "autoimmune" disease. Supplemental thyroid so easily normalizes estrogen and the immune system that it, with progesterone and pregnenolone and DHEA, should be considered as the cure for autoimmune diseases, including thyroiditis—at least until someone finds an "autoimmune" disease that doesn't respond to a balancing of these hormones.

Breast discomfort and even the secretion of milk not associated with pregnancy or parturition, produced by excess prolactin, can often be relieved by thyroid, especially when taken with vitamins A and E. The incidence of breast cancer is high in hypothyroid regions. Excess prolactin and excess estrogen are associated with each other, with breast cancer, and with hypothyroidism.

Most physicians know how to test the Achilles tendon reflex, but believe it is a poor indicator of thyroid function. Often, this is because they have observed the reflex contraction itself, rather than the relaxation rate, which gives a clear indication of the rate at which energy is regenerated in the muscle. The "T wave" or repolarization wave in the electrocardiogram gives a similar indication of lagging energy production in hypothyroidism. Magnesium retention by cells is dependent on thyroid hormone, and is essential for cell relaxation.

The rate of energy restoration is relevant to the tired brain, too. Insomnia is the most commonly troublesome symptom of menopause, and it usually responds immediately to a small bedtime dose of T_3, just as T_3 rapidly restores the normal quick relaxation rate to the calf muscles and heart muscle. (Two or three grams of sodium chloride taken at bed-time in a little broth, or juice or water, has a strong sleep inducing effect; it lowers adrenaline, promotes glucose absorption by the intestine, and has other antistress actions, including "sparing" magnesium.)

Thyroid permits energy to be produced efficiently from glucose, and hypothyroidism causes glucose waste leading to hypoglycemia, which in turn leads to excessive secretion of adrenaline. Adrenaline, like the synthetic drugs that mimic its actions, has been known to be toxic for many years. It mobilizes fatty acids from storage, and its most obvious toxicity is to the circulatory system.

The circulatory complications of diabetes were avoided in Broda Barnes' diabetic patients, who received thyroid supplements. In diabetes, glucose is unable to enter cells, and the body's response resembles that of hypoglycemia, secreting adrenaline and mobilizing fats from storage. Since a certain amount of intracellular glucose is needed before the liver can form T_3, diabetics, like hypoglycemics, or like anyone during starvation, are unable to activate the thyroid hormone.

Adrenaline secretion leads to cortisol secretion. The "Cushingoid" fat distribution, sudden balding, and other signs of hormone imbalance secondary to hypothyroidism are statistically associated with heart disease. Broda Barnes clearly showed the protective action of thyroid against heart disease.

Too much thyroid does cause enlargement of the heart. Meerson, and others, have shown that growth of the heart muscle is a normal process of adapting to an increased workload. In a more extreme situation, too much thyroid can cause relative starvation, arresting growth, by causing the tissues to "work" too intensely. When mice are given food containing 1 % thyroid by weight, they stop growing, but normal growth resumes if they are also given liver as a nutritional supplement. Rats that were given enough Armour thyroid to stop their growth (up to 0.7 % of their food) had bones that were slightly heavier than the bones of the rats on the normal diet that had grown at the normal rate. That is, even when the diet isn't adequate to sustain normal growth, hyperthyroidism doesn't necessarily cause osteoporosis. Very large doses of thyroxine, though, are not the same as hyperthyroidism. An often cited report on osteoporosis that was observed in a few women who were taking thyroxine, actually provided no clear data to support its conclusions, but it did illustrate two important fallacies: Failing adequately to take into account that women who take thyroid medication have a history of hypothyroidism, and ignoring that thyroxine reliably suppresses the pituitary TSH and thus decreases the T_3 secreted by the thyroid gland, but doesn't reliably increase the liver's formation of T_3. Hypothyroidism,

whether natural or promoted by administered thyroxine, retards bone remodeling and tissue repair in general. As hypothyroidism predisposes to excess cortisol effects, it must also be a common factor in "Cushingoid" osteoporosis.

When the thyroid is normal, vitamin A and cholesterol are used rapidly in forming progesterone. Carotene tends to accumulate in hypothyroidism, and it can bind to the cells of the corpus luteum, preventing the use of vitamin A to form progesterone. Adrenalin, cortisol, prolactin, and ACTH are likely to be elevated in hypothyroidism, and they have been proposed as inhibitors of ovulation or progesterone secretion. Estrogen is usually elevated in hypothyroidism, and can prevent implantation of the embryo, or cause miscarriage if implantation occurs. Adequate thyroid normalizes these anti-fertility factors, which is why it was considered the basic fertility hormone. It is also essential for the vitality of sperm cells.

Animals which are artificially made hypothyroid develop cystic ovaries, so it is reasonable to consider hypothyroidism as an important factor when women have cystic ovaries. Thyroid hormone's effects on all systems of the body—nervous, immune, digestive, excretory, respiratory, etc.—contribute to optimal fertility, and to the vitality of the offspring.

Exercise lowers the level of thyroid hormones, partly by accelerating their breakdown. The stress of winter appears to do the same thing, and most people (and animals) need much more thyroid in the winter than they do in the summer. Exercise lowers human (and some animals') fertility, and winter lowers animals' fertility. I think human fertility, as indicated by sperm count, for example, is likely to be lower in winter.

Because some estrogen is secreted in the bile, adequate fiber in the diet (oats, potato, or raw carrots, for example) and regular bowel function help to prevent the build-up of estrogen, which inhibits the thyroid. (Estrogen which has been excreted in the bile can be reabsorbed from the intestine if there is slow transit time and too little fiber.) A deficiency of B vitamins or protein is also known to prevent the liver from excreting estrogen. One of the ways in which starvation inhibits thyroid function is by damaging the liver function. Vegetarians are sometimes dangerously deficient in protein, and in that state the body is very resistant to thyroid hormone. Elevated serum calcium is probably one of the factors in creating a state of thyroid-resistance during stress.

Thyroxine can protect against lipid peroxidation, yet the hormone is essential for the normal oxidation of fat. One aspect of its "antioxidant" function is that it allows respiration in the mitochondria to consume the reduced (electron donor) substances, which otherwise can accumulate and be oxidized by stored iron, to start the free-radical attack on lipids.

There are many directly anti-thyroid substances, but the only directly thyroid-activating substances I know of are coconut oil, progesterone, and pregnenolone. The saturated fatty acids, especially the highly soluble smaller molecules found in coconut oil, probably tend to simply dilute and weaken the inhibition that is chronically exerted by the polyunsaturated fatty acids, but butyric acid seems to have some specific effects, such as facilitating the uptake of T_3 by nerve cells and shifting cells away from the expression of the stress-related proteins. Progesterone promotes the release of hormones from the thyroid gland, and by promoting the formation of glycogen, it probably supports the formation of T_3 by the liver. Pregnenolone, which is formed from cholesterol in the mitochondria, also normalizes thyroid function, probably partly by optimizing the balance of steroid hormones, and partly by stabilizing the enzyme systems of the mitochondria.

Transdermal Progesterone for Premenstrual Syndrome

Townsend Letter for Doctors, November/December, 1983

For many years, Katharina Dalton[1] has studied the use of progesterone therapy for the premenstrual syndrome. A typical patient may require ten or more progesterone injections per month, more or less permanently. While this is feasible (at least in some countries) it is not comfortable or convenient, in some cases leads to serious reactions at the injection sites, and in the United States would be too expensive for general use. When the syndrome is disabling, even the burden of frequent and expensive injections is usually seen as a welcome alternative. However, a less expensive and more pleasant form of administration could make the therapy available to millions of women who are now disabled for one or more days each month. We are reporting here on what we believe to be a satisfactory alternative to the injection or implantation of progesterone, namely, a solution of progesterone and vegetable oil in a lotion or "cold cream" base for transdermal use.

After animal experiments revealed that progesterone in vegetable oil was absorbed effectively through the skin, in 1977 we began experiments with women who suffered from the premenstrual syndrome.

The effectiveness of the transdermal (absorption) route of administration varies with the individual, but compares favorably with injections in the amount assimilated. Thickness of skin or degree of circulation in the skin (these can be very abnormal in hypothyroidism, for example) and the amount of adipose tissue apparently make some difference in the rate of absorption and response. When a small daily dose (e.g., 5 or 10 mg) is sufficient, this can be taken as about 250 mg of a 3 % cream rubbed into the throat, where it leaves no noticeable oiliness after a few minutes. For large doses, the appropriate amount can be applied to a larger area of skin after a hot bath, once or twice a day if necessary.

We have used transdermal progesterone therapy in two hundred women suffering from the full range of premenstrual symptoms, including migraine, acne, depression, mastalgia, edema, and lethargy, and we found that nearly all of the women, applying the lotion themselves, are able to find the appropriate dosage for controlling their symptoms. Occasionally, thyroid therapy, weight reduction, or change in some aspect

of life-style is necessary for complete relief from symptoms. We have learned that it is necessary to be very explicit in describing the amounts that can be used, while leaving it up to the patient to find the dose which controls her symptoms, because some women have an exaggerated idea of the power of a "hormone." We have learned, when some women said the progesterone had no effect, that they were applying it as sparingly as they would a rare perfume, just touching it to their wrists.

Another problem we have encountered is that a few women have trouble understanding how, if their edema is caused by "hormones," a "hormone" could relieve the edema. We have usually solved such problems by applying one dose (sometimes using a 25 % solution) in the office, and waiting thirty or forty minutes to make sure that it was large enough to take effect. Once having felt sudden relief from this "cold cream," it is easier for the patient to understand how it should be used.

Unfortunately, many of the solvents which hold progesterone stably in a concentrated solution are highly allergenic. Injectable progesterone in oil could be used transdermally except for this problem. Progesterone can be removed from an injectable water suspension, and dissolved in warm olive or almond oil for transdermal use in patients who react to other solvents.

Unsaturated Oils Have Deleterious Effects

Townsend Letter for Doctors, May, 1988

I agree with your recent remarks about directing criticism mainly toward the errors of conventional medicine, because the biggest problems exist within the orthodox and government-established medical system. As you said, people should not be put down because of their degrees, and for that reason I avoid putting letters after names, except when there is a reason for it. However, I got a letter from Charlotte Gerson criticizing me for failing to mention Budwig's degree. Since the other degrees (including mine) were editorially added to my letter, it wasn't my intention to slight Budwig for being degree deficient.

However, Charlotte Gerson also says that I made "a number of statements which are not defensible," but doesn't seem to understand what I said. I am aware that linseed oil has been used by Mexican physicians to treat cancer at least since 1939, and that it can be toxic to cancer cells (though probably less toxic than to normal cells),[†] and that its laxative action is plausibly effective in treating constipated cancer patients. My primary criticism is that people who get on the big marketing bandwagon (whether the product is linseed oil or germanium or iron supplements) so often—as in the Udo Erasmus book—appear to systematically lead attention away from the possible dangers of their product.

The "deleterious effects of unsaturated oils" have been clearly established and are recognized by everyone working in the field. They are not "supposed" and are not merely "discussed" subject to disproof "by others." Many people are now investigating a variety of theories that attempt to explain the specific nature of the toxicity.

The opinions credited to Budwig by Erasmus suggest ignorance of organic chemistry and biochemistry. If someone takes Dr. Budwig's ideas seriously, TL/D should invite her to explain them herself.

Without knowing more about the publication details of the new version of the book, *Fifty Cases*, and the letter that Max Gerson supposedly wrote to Schweitzer, I wouldn't want to analyze all of the ideas ascribed to him. The original book, which I believe was reprinted several

[†] Cancer cells are rich in antioxidants which protect them against free radicals.[1]

times without changes, even after his death, was a coherent scientific document. Posthumous "new editions" always raise questions.

Using Sunlight to Sustain Life

Townsend Letter for Doctors, June, 1996

Q: You mention sunlight as beneficial to your health. How?

For example, it can cure depression, improve immunity, stimulate our metabolism while decreasing food craving, and increase our intelligence.

Although exposure to sun does contribute to aging of the skin, people who spend years working outdoors have a reduced incidence of cancer of internal organs. For many years, it has been known that the death rate increases during the winter months and also increases at night (winter or summer). Most deaths occur just before dawn when the body is in its least efficient state. It is just in the last few decades that we have been learning the reasons for this beneficial effect of light. It turns out that daylight stimulates our ability to use oxygen for energy production, and protects our tissues from some of the free-radical toxins that are produced by normal metabolism, by stress, or by radiation.

While ultraviolet light, and even blue light, tend to suppress our cells' ability to produce energy, those types of light penetrate only a short distance into living tissue, and so it is mainly the skin which is damaged by too much sunlight. Since blood does circulate in the layers of skin which receive ultraviolet rays, prolonged sun exposure can damage the immune system by injuring white blood cells, but usually the stimulating effect of the other types of light that penetrate more deeply offset this effect on the immune system.

Many health food stores are now selling melatonin, to reduce sleep and "prevent cancer." They have taken some information out of context, and don't realize how dangerous melatonin is. It makes the brain sluggish, causes the sex organs to shrink, and damages immunity by shrinking the thymus gland. It is the hormone of darkness and winter, and is produced in the pineal gland by any stress which increases adrenalin. Adequate sun light suppresses the formation of melatonin.

This means that the immune system is most responsive in the summer, when days are long. Daylight stops the stress reaction, and protects our immune system.

Q: Doesn't exposure to the sun age you?

This effect is variable, and depends on our hormones and diet.

The unsaturated oils have been identified as a major factor in skin aging. For example, two groups of rabbits were fed diets containing either corn oil or coconut oil, and their backs were shaved, so sunlight could fall directly onto their skin. The animals that ate corn oil developed prematurely wrinkled skin, while the animals that ate coconut oil didn't show any harm from the sun exposure. In a study at the University of California, photographs of two groups of people were selected, pairing people of the same age, one who had eaten an unsaturated fat rich diet, the other who had eaten a diet low in unsaturated fats. A panel of judges was asked to sort them by their apparent ages, and the subjects who consumed larger amounts of the unsaturated oils were consistently judged to be older than those who ate less, showing the same age-accelerating effects of the unsaturated oils that were demonstrated by the rabbit experiments.

While it is important to avoid overexposure to ultraviolet light, the skin damage that we identify with aging is largely a product of our diet.

Q: Don't you have to avoid sunlight because of skin cancer?

The type of skin cancer which is clearly caused by sunlight is a relatively harmless type of cancer, which appears only in sun-damaged skin. Melanoma, which is often called a skin cancer, because it sometimes begins in moles, does not have such a simple relationship to sunlight, and its incidence is significantly increased by the use of estrogen.

It is often said that the great increase in deaths from melanoma during the last 60 years has been caused by an increased popularity of sunbathing, but during the same time there has been a great increase in the incidence of cancer of the prostate, which is in a location that gets very little exposure to light. What these two cancers have in common is a sensitivity to estrogen, and it is during this same period of time that we have been exposed to increased amounts of estrogen-like chemicals

in the environment as a result of industrial pollution: Dioxins, phenols, chlorinated hydrocarbons, DDT, smoke, etc. It is likely that these cancers (and others) are caused by the estrogenic pollutants.

The incidence of melanoma is consistently lower at greater elevations, where ultraviolet light is more intense, than at lower elevations. It is common for melanoma to develop on relatively shaded areas, including the middle of the back and the inside of the thigh, unlike the ordinary less malignant skin cancers, which develop most often on the forehead, nose, ear, cheek, and lip, where sun exposure is greatest. People who work outside have a low incidence of melanoma according to some studies, and this is sometimes said to be because they don't get sunburned, as pale people do when they spend time in the sun after being indoors for long periods. Sunburn does cause freckling, which is a clumping of pigment cells, but recent studies show that children who get sunburned are not at increased risk for melanoma. Sunburn causes complex changes in the tissue, including weakened immunity.

To avoid the aging and immuno- suppressive side effects of sunlight, it seems best for sunlight to come through a window glass which removes most of the ultraviolet light, and some of the blue light. Plastic film is available which contains copper that removes this harmful part of sunlight, and can be applied to ordinary window glass. Sitting in sunlight coming through a window of this sort, for short times during the day, is very protective. Besides protecting against cancer, it helps to keep the mood and energy level high, by keeping melatonin low and stimulating metabolism.

Recently, the polyunsaturated oils have been identified as the main thing in cells that radiation interacts with, to cause cellular damage. Vitamin E, taken internally or even applied to the skin, has been found to reduce the damage produced by exposure to ultraviolet radiation, which is logical, since it interrupts the chain reactions of toxic free-radicals produced when unsaturated oils are oxidized by radiation or other injury. Aspirin has been found to have a similar effect in reducing the harmful effects which develop in the skin after sunlight overexposure. Coconut oil has been used for generations in "suntan lotions," and whether it is absorbed through the skin or eaten as a food, it clearly has a protective antioxidant function. Carotene seems to work with vitamin E in the skin to reduce injury by ultraviolet radiation.

Caffeine also has shown a protective action against radiation, but its mechanism of action isn't clearly understood.

Q: Why not use sun-blockers, so you can get light without getting burned?

If a sunscreen lotion is based on the use of an opaque reflective material, such as zinc oxide or titanium oxide, that substance remains mostly on the surface of the skin. This should make it fairly harmless, though it is possible that traces of titanium could be absorbed with oils into the skin, where it could be made toxic by interaction with ultraviolet rays.

However, other chemicals used in the sun screen lotions, such as PABA derivatives, also react dangerously with light, and are easily absorbed in significant quantities into the deeper layers of the skin, where they can cause mutations.

For example, several recent studies have found that the sun-blockers, which decrease the ordinary skin damage caused by ultraviolet rays, actually increase the risk of developing melanoma, by causing mutations when the cells' chromosomes interact with the sunscreen and the light. (Something similar happens in the disease, porphyria. A pigment that accumulates causes the skin to become very sensitive to the sun. Estrogen is known to intensify the disease.)

Even natural colored compounds, which have sometimes been used in suntan lotions, should be avoided, since they might be able to transmit the energy of light to the chromosomes, causing mutations. Radiation from the sun reacts with the unsaturated fats you have eaten to cause oxidative damage to skin cells. Vitamin E, vitamin A and carotene are antioxidants that prevent skin cell damage, when they are taken internally or applied to the surface of the skin. None of these causes any harmful effects in the sun.

Aspirin reduces the iron content of the blood serum, and also inhibits the formation of the sometimes-toxic prostaglandins from fatty acids. Coconut oil is very resistant to radiation damage and, like vitamin E, tends to stop the chain reactions that occur in unsaturated fats. The old formula for suntan oil, coconut oil with iodine, might turn out to be a safe sunscreen, since the brown iodine absorbs light, as other "U.V. blockers" do, but iodine is also an effective chain breaker that inactivates free

radicals, and it can't be absorbed into cells in its brown form. It doesn't have the potential for causing cancer that the popular sunscreens do.

Q: Is sunlight still beneficial if you use a safe sun blocker?

The popular chemical sun blockers are meant to stop the ultraviolet rays. If they can do that, without increasing the risk of melanoma, then they are very beneficial, because this will allow you to get a long exposure to direct sunlight, which penetrates deeply and has an anti-stress effect. But so far, there is no research that shows any of the chemical ultraviolet blockers is safe.

Q: Why do people seem to get sicker in the wintertime, often right after Christmas?

Nights are much longer in the winter, and even in the summer, death rates are higher during the night than in daytime. December 21 is the day with the fewest hours of sunlight, but the cumulative damage of prolonged darkness reaches its peak about a month later. Cold temperatures do have some harmful effects, but by keeping people indoors, or bundled up in thick clothing, cold weather also causes us to get very little exposure to sunlight. Winter sickness is mainly the result of a "light deficiency."

When young sailors spent 6 months in the continuous polar night of Antarctica, they developed the same signs of nocturnal stress that are common in old people during the night. Many old people habitually get up before dawn, because they find it impossible to stay asleep. Even healthy young people (and animals) experience some degree of nocturnal stress as soon as the light is turned off at night, and their body responds with an increased production of adrenalin and cortisol.

The energy-producing part of cells, the mitochondrion, shows signs of being increasingly damaged as the night progresses, but they are gradually restored to their normal condition during the daytime light hours. This means that our greatest ability to resist stress is in the late afternoon, and we are most susceptible to injury at dawn. In the winter, nights are long and days are short, so we experience a cumulative increase in our susceptibility to stress-injury during the winter months.

The light which penetrates deeply into our tissues (mainly orange and red light) is able to improve the efficiency of energy production' and to suppress the toxic free-radicals that are always being formed in cells.

Q: Can you get enough sunlight during the summer to hold you through the winter?

No, many of the beneficial effects of bright light disappear during just a few hours of darkness, though the restoration of our tissues that happens during the summer puts us into a better state for surviving the winter, for example by allowing massive regeneration of the thymus to occur. (This occurs in adults, not just in children. The idea that the thymus disappears after puberty is based on autopsies. If a person lives for even 3 hours after an accident or the onset of sickness, the thymus has had time to shrink.)

Frequent short exposures to bright light is almost as valuable as continuous sunlight, and it is less likely to cause skin aging.

Q: How much sunlight do we need a day for general health?

If artificial light is bright enough, it is as effective as sunlight at stopping the stress reaction, but people seldom use lights that are bright enough. Generally, people and animals are healthier when days are longer than 12 hours, that is, after March 21 and before September 20. When days are shorter than 12 hours, artificial lights should be used from sunset until bedtime, but the greatest brightness probably doesn't have to be continuous.

Studies on isolated organs and tissues suggest that a few seconds of penetrating bright light are enough to break the free radical chain reactions, slowing the production of toxic substances, which tend to increase in concentration during nocturnal stress. A few seconds' exposure to the direct light of ten 150 Watt incandescent bulbs, for just a few minutes every two or three hours, might provide more effective protection than continuous exposure to a single 100 Watt light.

Glossary

Mutations are changes in DNA molecules which can kill cells, or accelerate their aging, or contribute to the development of cancer. Cellular respiration: the ability of cells to consume oxygen and produce useful biological energy.

Free radicals are parts of molecules that can be produced by radiation (including sunlight), which contribute to cells' aging, cancer, and mutations.

The thymus gland is an essential part of our immune system, and it shrinks when we don't get enough light.

Melatonin, or pineal hormone: the pineal gland in the brain responds to an absence of light (or to any stress which increases the adrenalin systems) by secreting a hormone called melatonin, which lightens the skin, makes the brain sluggish, turns off thyroid and progesterone production, and suppresses immunity and fertility.

Immunosuppression refers to any process that lowers the efficiency of our immune system, such as stress, radiation, or poisoning.

Summary

1. In fall and winter, use very bright incandescent lights daily from sunset until bedtime.

2. Expose as much skin as possible to the bright light; even a minute is better than nothing. Thin, light-colored clothing transmits a considerable amount of light.

3. Infrared bulbs, with clear glass, are especially beneficial. Special low temperature red lights are available.

4. It is better to get your sunlight through windows, because it has less ultraviolet light than direct sunlight.

5. Don't use sun-blocking lotions, other than the simply reflective type (zinc oxide or titanium oxide).

6. Decrease the use of unsaturated oils in the diet, and use coconut oil as food and also on the skin during exposure to direct sunlight.

7. Vitamin E and aspirin reduce the harmful effects of sunburn, even when used after exposure to the sun, they can be applied topically to the burned skin. Vitamin E often contains some soy oil, so I recommend small doses of about 100 mg per day.

Vitamin A Toxicity

Townsend Letter for Doctors, October, 1985

YOU printed a letter to the editor regarding vitamin A; I've been tracking down vitamin A scare stories for years, and when I wrote to the researcher mentioned, he denied working on vitamin A.

In 1974 there was a well circulated rumor, in Washington and Oregon, that vitamin A had caused blindness. I traced the story to a professor at the University of Oregon Medical School, but she refused to talk to me about it.

I think the symptoms associated with moderate amounts of vitamin A in susceptible people are the result of temporary suppression of thyroid function, which can result from an excess of any unsaturated oil. Vitamin E, which spares vitamin A, has a powerful effect in preventing toxicity from large doses of vitamin A. In traditional diets, people who ate fish livers also ate fish thyroids.

The three big dangers in the U.S. diet are iron supplementation, excess of unsaturated oils, and sodium restriction. If you would like a review of research on these dangers, I would be glad to write it up.

Response to "A New Look at the Meaning of Reality"

Science News, Volume 99, Number 26, June, 1971

YOUR article, "A New Look at the Meaning of Reality,"[1] was interesting, but uninformed. Some criticisms: These ideas are not so new, at least when compared with what you call "traditional behaviorism." You seem to be trying to give the impression that these humanistic psychologists are emotional rebels against staid, sane and scientific traditionalists like Skinner, and that a theory is just now being created for them.

Kurt Goldstein (The Organism) apparently coined the phrase "self actualization," which was central to Maslow's very biological but also social psychology. Whitehead and the Gestalt psychologists showed several decades ago that consciousness shouldn't be thrown out of biology and psychology. Carl Rogers (e.g., *Client-Centered Therapy*, 1951) did very coherent theoretical as well as sound empirical work which led to the interest in group therapy and the awareness of the social implications of therapy. Merleau-Ponty and Michael Polanyi have provided very broad critiques of the pseudo-objectivity that Laing refers to.

Newspaper Excerpts

A la Carnegie

Eugene Register-Guard, November 15, 1984

THE Election Day announcement that the U.S. government is considering an invasion of Nicaragua was reported in the Wednesday *Register-Guard*,[†] which also editorially advised readers that "American compassion cannot prevent death through starvation…in famine-ridden countries…" yet pointed out that they could relieve their consciences by supporting soup-kitchen charities at home and abroad.

After your endorsement of Reagan, I suppose you feel the way Andrew Carnegie did when he said: "To continue much longer with most of my thoughts wholly upon the way to make more money in the shortest time, must degrade me beyond hope of permanent recovery."

Your editorial reaction is classical. Harming people who are attempting to feed themselves, and then publicly advocating "charity."

Two hundred years ago, such deceit was understood by honest people. William Blake wrote: "Pity would be nor more if we did not make somebody poor."

The charitable Carnegie Foundation was a pioneer in attempts to eliminate poverty by eliminating the poor. Their theory was that poverty was genetic. What is your theory of poverty? And why do you believe American compassion couldn't eliminate starvation?

If compassion consisted of withdrawing military support from brutal dictatorships around the world, people could begin to feed themselves.

It is no threat to me that Nicaraguans are learning to read and to cooperate with each other in overcoming poverty. Unfortunately, it seems to threaten Reagan and his supporters.

Almost Anyone

Eugene Register-Guard, October 15, 1976

PRO-NUCLEAR scientists, especially when their income depends on it, can behave oddly. In the 1950s, the program that measured bomb fallout was named "Project Sunshine," and some government scientists even claimed that fallout was good for us, "because radiation produced evolution." At least, they assured us,

[†] "Millions Are Starving," *Eugene Register-Guard*, November 7, 1984.

a little radiation wasn't harmful. Some "experts" still claim that the Hiroshima bomb didn't cause measurable genetic harm, but to reach this conclusion, people who were upwind from the explosion have to be averaged in.

The experts in nuclear energy often find it profitable to disregard the public's safety. More than 60,000 drums of radioactive waste were dumped in the ocean near the U.S. coasts, and after years of such disposal, divers investigated and found the barrels had been crushed by pressure, allowing the radioactive material to escape. Could this be considered "accidental" pollution? According to "Industrial Research," nuclear accidents have been increasing recently; however, much pollution is "permissible," rather than accidental. One government plant measures its daily emissions in terms of pounds of uranium.

Establishment physicists claim that their knowledge is complete enough to prevent miscalculations, but a State Department official has pointed out that nuclear test blasts have been unpredictable in size. Anderson and Spangler have presented evidence which contradicts the basic assumption on which nuclear reaction rates are calculated.

Everyone in the world is going to be involved in the outcome of our nuclear energy decisions, and the way many physicists are acting, almost anyone's opinion seems more reliable.

Bad Partnership

Eugene Register-Guard, March 30, 1985

YOUR article[†] discussing a conspiracy to promote the use of poison sprays, illuminates a more general problem. There is a trend toward a kind of partnership between some big universities and corporations which use new technologies; the people involved assure us that this trend will benefit the public—the consumers—but there is a good reason to doubt their objectivity and their correctness.

A Central California farmer who changed from chemical to organic methods, and now sells most of his products competitively to the ordinary supermarkets, has pointed out that the state universities which have spent so much public money to promote the agricultural methods favored by the chemical industry had absolutely no information to offer him to help in his conversion to completely natural methods. By eliminating the use of expensive chemicals, he saved enough to compete effectively in

[†] Bill Bishop, "State Accused of 'Spray Scam'," *Eugene Register-Guard*, March 15, 1985.

the market, in spite of the large research establishment which works closely with his competitors.

How much more cheaply could he produce food if he could have the advantage of research financed largely by the public?

If the state universities act as agents of the chemical industry, should they receive public money? Public finance should function as a counter-balance to the private money which buys the research it wants. Entire institutions can be swayed by the financial leverage of their "patrons."

When professors, who are agents of the state, accept any research funds from private industry, and then participate in any government decision which affects the profits of that industry, it certainly doesn't look good…

Ban Lead

Eugene Register-Guard, July 13, 1977

LEAD pollution can cause mental retardation, hyperkinetic behavior disorders, anemia, bone disease, and accelerated aging and degeneration of various tissues. Children are most vulnerable to lead poisoning. Leaded gasoline is the main source of lead pollution.

Some cities have banned the use of lead in gasoline. Why hasn't Eugene?

Dangerous Therapy

Eugene Register-Guard, May 23, 1985

I hope that the kind of information Sarah Stewart provides in her long reply to Mr. Frank's letter[†] is not the kind of information that doctors give to patients in obtaining their "informed consent."

In such drastic and permanent "therapies" as electroconvulsion and "leukotomy" or "psychosurgery," practically no properly controlled studies have been done. In one controlled study, the electrodes were applied to the patients' legs, instead of to the head, and the beneficial effects were just as good—and the risk of brain damage was obviously less. Physicians are careful to warn the public of the need for controlled studies before therapies using natural substances can be accepted; shouldn't removal of part of the brain have an equivalent scientific evaluation? The judgment of the person who administers the treatment is often accepted in evaluating "psychosurgery."

The machines for administering electroshock were required by

[†] Sarah Stewart, "Mental Health Care has Improved," *Eugene Register-Guard*, May 17, 1985.

law to be evaluated by the FDA. It placed them in the highest risk category, based on health risks including brain damage. By law, devices in that category were to be removed from the market if investigation didn't establish their safety. They remain in that category, but the FDA has not acted, as the law would seem to require.

The regulatory agencies are now acting flagrantly for the benefit of the big economic interests, and against the interests of the consumers. It would be nice if we could return to the rule of law.

Find the Facts

Eugene Register-Guard, June 24, 1977

IF fluoridation proponents have such a high regard for the public that they will prescribe and administer mass medication for them, and such a high estimation of the public intelligence that they believe medical and dental issues should be resolved by a public vote, then it would seem that they should have enough respect for the public intelligence to participate in some form of a public debate or at least a presentation of the actual facts in support of their position.

Since it seems that no proponent is willing to come right out and cite the particular scientific publications which support their position, and since it seems that there is no dentist or physician in this area who is willing to defend fluoridation in a public debate, and since Eugene magazine has already published enough information to make many people question the scientific competence of the fluoridation proponents, isn't it the responsibility of the *Register-Guard* to present a detailed discussion of the evidence which is claimed to demonstrate the efficacy and safety of fluoridation?

If the proponents resort to the argument that our small (public) minds couldn't understand and evaluate such scientific issues, then they are asking the public to accept their "professional authority." It might take some work to find and analyze the facts in support of fluoridation, the facts which are vaguely referred to by the advocates of fluoridation, but I think the public deserves a chance to see, in the Register-Guard, the facts on which the health professionals are basing their "authoritative" judgments.

† Allan Winkler, "History of the Atom Bomb Does not Explain its Initial Use," *Eugene Register-Guard*, July 22, 1982.

German Connection

Eugene Register-Guard, July 28, 1982

Allan Winkler's article† on Truman's use of the atomic bomb against Japan devotes some space to the question of whether U.S. policy toward the Soviet Union significantly influenced Truman's decision to incinerate several hundred thousand civilians. Before drawing his conclusion, I think he should have mentioned that Truman was known to be so anti-Soviet that he advocated supporting Hitler in his attempt to destroy the Soviet Union, and that the big-city Democratic party bosses, who were instrumental in getting Truman the 1944 nomination, and the presidency, also favored Hitler. Roosevelt and Vice President Wallace were working to insure good post-war relations between the U.S. and the Soviet Union, and this was known to be a major reason for dumping Wallace and choosing Truman. The maneuvering was so obvious that Stalin believed Roosevelt was assassinated to implement the new policy at a crucial time.

With the recent revelations of the secret importation of large numbers of fascist war criminals into this country, and the German connections of people who became prominent in our Cold War government (such as the Dulles brothers), Winkler's presentation of the context for the first use of the atomic bomb really seems inadequate.

Gossip Unfounded

Oregon Daily Emerald, December 15, 1975

I was asked by the assistant director of the SEARCH program to help with the organization and teaching of a class in nutrition. The student who was helping to get a department's approval encountered the explanation from a department source that I would not be allowed to teach it because I advocated "Adelle Davis' ideas." He said that they "know where" I "get my information." As far as I know, I have never talked to anyone from that department, so they could have no proper basis for knowing where my information "comes from." (Much of my information does come from an underground source, the subterranean science library at the University of Oregon.)

The fact is that I have never "taught Adelle Davis' ideas," and have rarely mentioned her books in a class, because I disagree with some of her emphasis, and feel that her books are not organized in a way that would make them easy to use in a class. However, I consider her to have been infinitely more

respectable than the envious nutritionists who have called her a quack.

This kind of unfounded gossip may be normal academic ethics at the University of Oregon, but I have no reason to tolerate the dissemination of misinformation about myself (or about Adelle Davis or Linus Pauling or Rodger Williams), so I am requesting that those statements either be retracted or defended in a public forum.

Since I was accused of teaching things that were "not true," I think the accuser has the obligation of meeting me in a public debate on those issues, or of admitting his error.

Health Frauds

Eugene Register-Guard, November 16, 1985

THE recent article[†] about the National Council Against Health Fraud might raise a person's suspicions, because of the freakish and probably trivial nature of the frauds mentioned. The immense problems they failed to mention suggest that they might be acting as a front for the drug industry.

Legal drugs for arthritis and cancer are worth several billion dollars annually. We are often told that more and more people are being cured of cancer each year, yet each year the cancer death rate increases. Is deception involved?...

The most extensively used and advertised "health food" is liquid vegetable oil; there has never been evidence that polyunsaturated oils improve anyone's health, beyond the trace amounts required as essential nutrients, and there is very clear evidence that large amounts are profoundly toxic. Is the huge food oil industry engaged in a dangerous health fraud?

In recent years clear evidence has emerged implicating supplemental iron in carcinogenesis. Do the drug companies who promote iron supplements warn the public about the danger of leukemia and other cancers? Does their advertising constitute a dangerous and deceptive health practice?

If a major drug for treating asthma contains metabisulfite, known to kill some people with asthma, should the public be warned? When a major medical journal, getting money for advertising the product, refuses to print a letter warning of the danger, is the health fraud council willing to investigate?

[†] Bill Bishop, "Oregonians Form Group to Combat Health Fraud," *Eugene Register-Guard*, November 5, 1985.

Undoubtedly the algae dealers are easier, more entertaining targets, but the absence of all of the biggest health deceptions from their list seems to say something about the group's real purpose.

Humanities Stifled

Eugene Register-Guard, April 13, 1982

Fred Crafts' article[†] reports that the Committee on Arts and Humanities intends to establish better relations between campus and city and to improve their promotion and marketing of the humanities.

The boring sameness of viewpoint which we find in the academic humanities is not because the subjects have some intrinsic lack of "momentum," as suggested in the article. The humanities are potentially so important, so exciting, so disruptive, that they have been deliberately stifled…

If the "humanities" are to be revived, it will not be by giving lectures to Rotary clubs. It will be because the "humanists" begin to take positions of human significance. Opposition to plans for nuclear war, opposition to militarism itself, opposition to oppressive legislation such as SB 1630, opposition to policies which impoverish millions of people, opposition to policies which make higher education impossible for a large part of the population, opposition to academic policies which allow tens of millions of people to become so gullible that they can be victimized by economic theories that were already discredited more than 50 years ago—these are positions which should grow naturally out of the humanities. If the universities take credit for intellectual achievement, they have to take blame for the production of a gullible generation. If the "humanists" start acting like human beings who are imbued with the great values of humanity, and begin criticizing, thinking, and imagining, instead of conforming, then the humanities can be revived.

Ill-Informed Statement

Eugene Register-Guard, February 21, 1991

I hope someone at Pope & Talbot Inc. is embarassed when they realize that the statement on dioxins they authorized Dr. Robert Loomis to make on their behalf[‡] is not only impolite and misleading (which

[†] Fred Craft, "Bringing Revival to the Humanities," *Eugene Register-Guard*, April 1, 1982.

[‡] Robert Loomis, "Activists in a Hurry to Eliminate Dioxin," *Eugene Register-Guard*, February 14, 1991.

might have been their intention) but also so ill-informed that he is probably going to feel obligated to retract parts of it.

If a student of mine had submitted that composition to me, I would have returned it ungraded for reconsideration and revision. If I were associated with Pacific Hospital Association, I would want to check Loomis' background in chemistry, epidemiology and toxicology. I suspect that many high school students are going to be submitting their detailed refutations of the physician's statement.

Impact Unknown

Eugene Register-Guard, April 27, 1988

ACCORDING to your recent article,[†] the cheif of the U.S. Forest Service says he doesn't know what ancient trees are. Many people would acknowledge that we really don't know very much about the ancient trees and how they related to the world around them, but almost any educated person would believe it is not proper to destroy something which you don't understand. Foresters are not educated to serve the interests of humanity in general, or to work for the good of our biosphere, or even for the U.S. national interest; rather, they are trained to serve the interests of the corporations which use trees.

The true environmental impact of cutting ancient trees is not fully known, and can't be known until better research is done. It would be reasonable to have a moratorium on cutting ancient forests, while research continues.

Forests of ancient trees are the greatest concentration of biomass anywhere on Earth. An ancient forest often has 100 times more biomass than a "young and productive" forest. The forest biomass is not inert, like a coal deposit, but contains a large quantity of exchangeable water, which allows a forest of giant trees to stabalize humidity, temperature, and even percipitation and climate in general. In areas which have long recorded history, it is clear that deforestation has greatly increased the frequency of droughts. Oregon and California are now beginning to experience what has happened earlier in other areas, including Africa, India, and Russia. The same destablization which produces droughts can also increase the frequency and intensity of flooding.

Taking short-term profits at the expense of long-range viability should no longer be an option. We

[†] *The Associated Press*, "Forest Service Chief Asked: 'Are You Stealing Our Heritage?'," *Eugene Register-Guard*, April 15, 1988.

need new public institutions with a broader view of the stewardship of resources.

Irresponsible Appeal

Oregon Daily Emerald, April 16, 1975

SINCE Senator Morse always seemed to know more of the important facts than the rest of Congress put together, Horn's foolish comment in the fund-raising letter[†] shows the extent to which a "non-political" university can go in trying to sell itself to the presumably reactionary prosperous alumni. Some alumni would prefer more responsible, literate appeals.

Look to the Future

Eugene Register-Guard, August 24, 1986

IN a historic human rights declaration, the United States pledged that all of its citizens had a right to a job, even if the government had to provide the jobs. Though it is common for the government to ignore pledges, contracts, laws, etc., economic realities still gice a kind of sanctity to the idea of full employment.

The recent discussions of "jobs vs. owls" often hinge on the fact of the desperate importance of jobs in a society which fails to provide decent opportunities for employment.

Another way to frame the same issue would be "unprecendented concentrations of wealth and power in the hands of the richest 0.5 %" vs. "preservation of enough of the natural biological world that regional or planetary systems do not go into irreversible decline."

The people who destroyed the coastal forests of Chile and created the Atacama desert didn't have the information with which to imagine the consequences of their actions. The people who removed the forests of Mexico's high plateau earlier in this century were foreigners whose grandchildren wouldn't have to see the barren, erroden, uninhabitable regions they created. But resident Oregonians, even if they are heirs to the multimillion-dollar fortunes made by the removal of Oregon's forests, should begin to develop their imaginations and consider what their grandchildren will think of their inheritances.

Maybe they could begin to imaginatively construct a future in which people have a right to jobs which do not degrade the physical, biological, social, and cultural environments.

[†] Alan Maltun, "Libeling the Dead," *Oregon Daily Emerald*, April 7, 1975.

Missed Point

Eugene Register-Guard, January 12, 1978

YOUR editorial on Robert Wright[†] seems to have missed the point he has repeatedly made in his letters; the bar, even more than the other professions, is established, in teh same sense that religion used to be established.

You say that "he hasn't passed the test that proves" he is well trained in law. Since you say that the courts have "properly limited his activities," "unless and until he does" pass the test, you seem to be saying that he has a right to take the test. Are you willing to say that openly? If not, I think that you are deliberately trying to confuse any reader who may not know that a person has to be "qualified" to take the test by having a law degree. (Since you refer to Wright as "self-trained" I assume he doesn't have a law degree.)

Professional schools are places of socialization and indoctrination. How many communists graduated from professional schools during the McCarthy era? How many disestablishmentarians, such as Wright, are allowed to enter Oregon's schools of law? Professions have value systems and ideologies built into them. Tests can in fact measure mere competency, but they are not very good at selecting individuals who have the proper values.

If tests "prove" the quality of training, as your editorial indicates, then Wright should be allowed to take the test, and to enter the bar if he passes it.

Do you disagree?

Money or Morality?

Eugene Register-Guard, July 25, 1985

PEOPLE working on the "Riverfront Park" project realize that military research might be done there, but claim that this is not an appropriate area for political or moral concerns. Richard Hersh, former university vice president for research said[‡] that it was an "oversight" that the project's directors were selected without a public announcement, and that "it never entered" his mind that the board is politically biased; but he admitted believing that Democrats are not "successful in business in this town."

According to the *Register-Guard*,[§] university administrators oppose extending the ban on clas-

[†] "The Wright Decision," *Eugene Register-Guard*, January 5, 1978.
[‡] Jim Boyd, "Science Park process is Criticized," *Eugene Register-Guard*, May 18, 1985.
[§] Lisa Strycker, "Strict Limit to Research is Rejected," *Eugene Register-Guard*, July 19, 1985.

sified research to the Riverfront Research Park: They are "reluctant to impose morals on a commercial enterprise." The vice president for research, John Moseley, says "there would not be a Riverfront Park" without classified research.

Forty years ago, many of the people who worked on the Manhattan Project realized that weapons-related science has a moral aspect. Hans Bethe, for example, now actively opposes the Strategic Defense Initiative, which is designed to give the illusion that the bombs can be used without fear of retaliation. The moral and political questions involved in secrets weapons or "defense" research are now clearer than they were when work was begun to produce the first nuclear bomb.

Our universities have always found it easier to work in the interests of big corporations than to support the interests of workers and ordinary people, because even state funds are influenced by business people. but when it openly becomes a choice between money and morality, President Olum should boldly take a stand against prostitution of the university.

Not Generous

Oregon Daily Emerald, January 22, 1973

THE aspect of Mailer that you condemn is what's best in him.[†]

You apparently have evidence that "good fucks" don't "make good babies," since you saved your wildest insults for that "pseudo-biological hypothesis" of Mailer's.

Before you can convincingly reject this and other sexual-political ideas of Mailer's, you should be able to dispose of the following observations, which have reported in recent years in medical, biological, and psychological journals:

Circulatory patterns are not the same in women who have a capacity for pleasure and orgasms, and those who don't.

Schizophrenia has autonomic and circulatory correlates.

Women who are schizophrenic at the time of conception abort male embryos much more than female embryos, and if their symptoms appear late, male babies are more likely to have defects: male embryos are known to be more sensitive to a variety of unhealthy uterine conditions.

Bad uterine conditions can cause defective babies, including small brains and mental retarda-

[†] (Regarding Barry Mitzman's comments on Mailer's "Catholicism.")
Barry Mitzman, "Mailer Converts—Almost," *Oregon Daily Emerald*, January 12, 1973.

tion, depending on when the trouble occurs, what it is, etc.

Improved uterine conditions—presumably the circulation—can improve the percentage of healthy and precocious babies.

The literature that may be relevant to this question is surprisingly large and varied—surprising, because our culture is ruled by an anti-biological dogma that denies any connection between physiology, emotion, and politics.

Your commitment to an abstract, anti-biological form of existentialism is fine for a bourgeois literary critic, but to imply that such a philosophy is the best hope for women is not very generous.

Nuclear Blackmail

Eugene Register-Guard, August 19, 1981

THE interior secretary's vision of our natural resources being consumed by the big corporations before Armageddon, and the Pentagon's increasing preparations for nuclear war, on the surface might suggest that this is a terminal administration, really preparing to wind things up forever. While it is true that some of our leaders lack common sense, I think their advisers and promoters have more "realistic" plans for the future.

The neutron bomb is not popular in Mexico. Many people realize that it would be a handy weapon to be used by a neighbor intent on invading and occupying their oil fields. If affairs don't go well for the U.S. in the Middle East, I think our policymakers will apply all necessary pressure to get as much oil as needed at a favorable price from Mexico. While the weapon could easily trigger nuclear war if used in Europe or Iran, I believe some policymakers would feel that it could be used in this hemisphere without threat of nuclear retaliation. For some Mexicans, deployment of that weapon in the U.S. constitutes nuclear blackmail and terrorism.

It is not in our interest to allow the neutron bomb to become another tool of the oil corporations.

Other Factors

Eugene Register-Guard, Novemeber 4, 1980

YOUR editorial[†] on declining scores on the Scholastic Aptitude Tests considered only educational and social factors as possibel causes. At a recent conference of military psychologists concerned about the mental quality of their recruits, I learned that some of them believe that the actual biological intelligence of Americans is dete-

[†] "SAT-Score Depression Persists," *Eugene Register-Guard*, October 24, 1980.

riorating because if factors such as malnutrition, food additives, and effects of the estrogen in birth control pills.

Estrogen excess in pregnancy, like a thyroid deficiency, has been known to damage the growing brain.

A study of nutrition in San Diego showed that 10% or more of the people born in that area are below the nutritional level at which brain damage is to be expected.

Shanklin and Hodin (in *Maternal Nutrition and Child Health*) have documented that medical practices which became widespread in the 1950s damage the brains of large numbers of babies.

Last year the government advised against the use of soy in baby "formulas," shortly after it was discovered that such vegetable oils can cause brain damage.

Because of the political and financial implications of these facts, many people are reluctant to discuss them publicly. I hope your next editorial on declining SAT scores will include among the possible causes "istrogenic and dietary brain damage during pregnancy and infancy."

Paid-off Press?

Eugene Register-Guard, January 17, 1979

YOUR editorial[†] hesitantly admits the plausability of Dorman's and Omeed's interpretation of the performance of the U.S. press in reporting events in Iran.

As I read the daily falsehoods in the *Associated Press* reports about the shah's opponents, I tried to imagine how and where such views might originate. One theory that has been proposed is that Christian reporters were blinded by religious prejudace. Another theory is that they were just lazy, and got their news only from the shah.

Several weeks ago, a long and apparently honest interview with Khomeini was broadcast by our public television network, but the false reports continued to be printed in U.S. papers. Khomeini said the U.S. was forcing Iran to spend its money on American weapons, preventing real economic development in Iran. This was interesting and important news, but as far as I can tell, it never became "news" in the U.S.

It was at that point that a third hypothesis occured to me: Maybe the *Associated Press* people in Iran are working for the CIA or the USIA. As you undoubtedly know,

[†] "Did the Press Miss the Boat in Iran?," *Eugene Register-Guard*, January 12, 1979.

the CIA has in the pas used reporters and editors, both at home and abroad, to plant "news" stories. (Wasn't it a president of the American Society of Newspaper Editors who said that CIA payoffs had brought shame onto the press?) According to a University of California professor, the shah has continually "paid off" large segments of the American media (with checks, copies of which were published). The CIA could find less embarrassing ways to adminster the funds. To protect many billions in oil sales to the U.S., and weapons sales to Iran, suppose $1 billion was diverted to the media: a thousand payoffs of $1 million each. Much less would do, I suppose…

Policy, or Myth?

Eugene Register-Guard, April 12, 1984

WHILE I was visiting friends recently, their 11-year-old son told me he favored Reagan's reelection, because of his "realism" in spending more on the military, and less on social services.

I asked why that was "realistic," and the child and his parents answered that the Soviets would invade us if we didn't have a strong military. I asked why they thought that, and they said, in unison, "That's their stated policy."

Since then, I have heard that idea repeatedly: "It's their stated policy," to invade us, etc.

I have tried to find when such a policy was stated, but haven't found anything in the history of Soviet foreign policy except statements in favor of peaceful coexistance and universal disarmament.

If there is, or has been, such a policy, it is of the interest that people like me are unable to find it. If there has been no such policy, then it is of great interest, socially and politically, that so many people believe in a myth.

It seems that we have two types of people; those who feel desperately threatened by the Soviet Union, and those who don't. I think this indicates that the mass media aren't doing a good job in presenting background information on current topics, such as the arms limitation talks. If U.S. foreign policy is based on a paranoid myth, even newspaper publishers ought to be worried.

Poor Leadership

Eugene Register-Guard, May 19, 1981

WHEN half the people are functionally illiterate, traditional and simplistic opinions have a natural tendency to flourish.

A self-interested politician will know how to tak eadvantage of the public's cultural backwardness.

When a state superintendent of schools acts like a common politician, our culture is sure to be degraded.

When Verne Duncan says[†] that he would prefer leaving to local school districts the issue of equal time for creationism in the science curriculum, I feel he is providing retrograde leadership. If a state superintendent of schools can't inform himself and take appropriate action on a matter of curriculum, what is his function?

Power Misplaced

Eugene Register-Guard, April 18, 1985

It's hard to understand how Congress, which was constitutionally given the responsibility for deciding when to declare war, can allow one man to launch the missles which could end the world. Especially when the man with this power is one who plans to honor the dead Nazi soldiers while ignoring their genocide, and who has forgotten even which World War he is talking about: According to columnist Ellen Goodman, he said, "I felt since the German people have very few alive that remember even the war and certainly none of them who were adults and participating in any way..."

I doubt that such a mentatlity would even be allowed to renew his driver's license in Oregon, but in the White House he is allowed access to the Doomsday button.

Program Not Experiment

Oregon Daily Emerald, February 18, 1969

A system of "free scholars" has existed in England for 700 years. The basis of an Oxford education is reading, with comprehensive examinations required after the residence period.

Oregon's new program for 20 students is a very small step in the right direction, but to call it "experimental" seems to insult the other 14,000 students who will not be admitted to the program, implying that it is dubious that even 20 students are really motivated by a desire to learn.

Granted that some of the University residents need custodial care, it is improper to attempt to combine the functions of discovery and learning with the confinement and entertainment of socially irresponsible people.

[†] Teresa Barker, "Board Lays Creationism to Rest," *Eugene Register-Guard*, May 12, 1981.

I propose, therefore, that Oregon State, or a similar institution, be given a purely custodial role, retaining all the authoritarian features of the German universities we have copied in the U.S. for 200 years (including grades and examinations every few weeks.) This would free the University to be a university, in which every student was expected to be a free scholar.

Psychedelic

Oregon Daily Emerald, March 8, 1973

TIM Leary stands up for human rights and human desires. He's in prison, and may not get out in the 20th century.

Richard Alpert, of the New Haven Railroad family, is free to travel anywhere in the capitalist world, spreading the old ruling-class lie that desire is bad for you, that simple, thoughtless, passive labor is a proper human role.

Alpert is the opiate of the hippies. By comparison, Tim Leary is psychedelic.

Racism and Ideology

Eugene Register-Guard, October 27, 1983

MARTIN Luther King gave increasing attention to opposing the Vietnam War in the months before his death. He was teaching the public that militarism, racism and poverty are interrelated. Many conservatives hated him for making such connections, and asserted that he was taking a "communist" position. Hundreds of editorial writers advised him to stick to the issue of race, arguing that to tie it to the then-popular war would hurt his cause.

Racism is an ideological issue. Your editorial writer says, "He wasn't fighting political ideologies, he was fighting racism." Reducing racism to a personal, non-political question is to obscure the truth, that racism has been, and continues to be, used as an ideological weapon to keep people divided, poor, and helpless.

When King was killed, he was supporting a garbage workers' strike. He urged unity in the struggle against poverty and the war. The issue of unity is so important that people like Senator Helms, Govenor Thomson, and Reagan try to cover it up. I hope the *Register-Guard* writer simply forgot the historical facts, and isn't deliberately contributing to the effort to counteract King's work.

SAT Misconceptions

Eugene Register-Guard, May 20, 1986

THE decline in SAT scores, and the tests themselves, are of less importance than the ideological conflicts they reveal. Your recent

editorial publicized only one side of the argument.

To explain the changes in terms of a new type of student in the high schools, and the response of teh schools to this new population, threatens to be used as an argument for elitist educational programs, and for a lower class education for the "poor class of students."

Accounting for the change in scores on the basis of inceraased numbers of poor students taking the tests doesn't account for the fact that the shaprest decline occured among the highest scorers. Several studies have looked for extrinsic causes—cultural or biological—to account for the changes. Related studies were done for the U.S. Navy, to account for the learning problems of their recruits. Some of these studies are pretty convincing scientifically, but they have not been well publicized, because they place the blame on various powerful institutions in out society, rather than on the poor segments of society—who, as the numbers show, are not where the biggest change has occured.

Stop the Fanatics

Eugene Register-Guard, August 22, 1984

In the 1950s, many high officials openly advocated a first-strike "preventive" war against the Soviet Union. Government documents made public in 1983 reveal that such a war was scheduled to begin in 1949, and was postponed when the Russians demonstrated that they too had nuclear weapons. Rescheduled for 1957, the plan was again changed when the Soviets produced the hydrogen bomb sooner than expected, and were not in the desired weak position.

Officials such as Dulles and Goldwater wanted the atomic bomb to be used even in Vietnam.

When he speaks seriously to religious groups, and when he jokes with his staff, our President reveals murderous and paranoid thoughts.

Seen in their historical context, those statements shock humanity. Seen against a background of increasingly militaristic anti-Soviet television programming, they appear to be part of a campaign to prepare the public for further "anti-communist" adventures against small nations, probably in Latin America.

When high officials can claim that Mexico is the center of subversion in this hemisphere, it is clear that our government is moving toward bigger things than just the invasion and permanent occupation of Grenada.

A landslide victory for Mondale might come in time to stop the fanatics.

Time to Recant

Eugene Register-Guard, July 23, 1984

THE editors of newspapers who endorse a candidate take upon themselves a responsibility for the outcome of his policies.

As a result of Reagan's policies, real production and the prosperity of most people hav edeclined. Oil prices are not to blame, because they have declined in this period. Other industrial countries moved ahead in these years.

The poorest and weakest people have suffered the most. According to Harvard's School of Public Health, infant deaths "skyrocketed" in Boston and other cities, rising 50 % in a single year of Reagan's administration—a rate of increase equaled only during famines and plagues, and never approached before in American history.

The promised balanced budget turned into more debt than had accumulated in all previous history.

The giant corporations have profited to an extent that is unique in history.

Those giant profits of the monopolies were nothing but a transfer of funds from most people—a mortgage—to a few people.

The wealth transferred in four years is a debt which will never be repaid. But newspapers and the editors who bear responsibility for Reagan's election in 1980 should gein now to make a small gesture to the country, recanting their endorsement.

Under U.S. Control

Eugene Register-Guard, August 2, 1983

IS it possible that our President has confused Central America with "Middle America," with Iowa? This could explain his statements about "our front yard." But it wouldn't explain his fabrication of stories about "outside aggression."

What we are seeing now in Central America is not an "East-West" competition, but rather the consequence of a radical shift in U.S. policy which occured in the spring of 1945.

Roosevelt's Good Neighbor Policy was moral and made economic sense for capitalist America. Roosevelt's administration saw both the Soviet Union and Latin America as "vast markets" to be developed.

With Roosevelt's death, his dream of world peace based on trade and on justice as he understood it was replaced by a different ideology. The new policy was shaped largely by John Foster

Dulles, who described himself as a "sadist" who "thirsts for confrontation" with the Soviets and with independence movements in Latin America.

In 1945, the phrase "under U.S. control" was reserved for private government memos. The present economic crisis is bringing that kind of thinking into the open.

A few historians (and eventually journalists) were instrumental in educating the U.S. public about the meaning and origin of the Indo-China war. Similar work must now be done regarding Latin America.

Voters Face Test

Eugene Register-Guard, October 15, 1988

America's journalists and teachers will soon have a chance to see how well they have informed the public, how well they have taught them to value democracy. There will be a sort of national quiz on November 8 to see whether the public can remember which candidate for president is the one who:

1) Said he would find a way to evade a Supreme Court ruling. 2) Denounced Medicare as "socialism." 3) Conspired to decieve a president-elect with distorted intelligence reports. 4) Had many opportunities to recieve information on criminal activities and treason in connection with his office, yet claims ignorance. 5) Advocates a presidency which is above the system of checks and balances. 6) Counts on the overwhelming support of extremist Orange County to win California and the presidency. 7) Doesn't talk about the national deficit, because he and his buddies are the creditors. 8) Praised Poland's union members, said Detroit could use Eastern European workers' skills, but despises America's unions. 9) Claims competence in intelligence, yet allowed fascists and anti-Semites to hold high positions in his campaign organization. 10) Called himself a Goldwater Republican and openly advocated use of atomic bombs in the Vietnam War.

Most of these items were casually reported in the *Register-Guard*, others in the *Los Angeles Times* and other major publications.

War Unpopular

Eugene Register-Guard, April 13, 1986

A few years ago, when Argentina was ruled by brutal mass murderers, they were active supporters of the Reagan-Contra war against Nicaragua. Now that democracy has returned to Argentina, that country agrees with every other democracy in Latin

America, and with practically every democracy in the world, that the United States should not expand the war in Central America by sending additional support to the Contras. Even dictatorships such as the Pinochet government of Chile are surprisingly reluctant to openly support Reagan's plan for a major war.

According to polls, most Americans ignore or reject the false information they are receiving from Reagan's propagandists regarding events in Central America, and also oppose enlarging the war.

Unfortunately, our U.S. Congress is humiliating itself, by allowing itself to be so evenly divided on the issue of interfering in Central America; allowing itself to be so easily manipulated by the pseudo-patriotic rhetoric coming from the White House and the State Department.

Which Revolution?

Eugene Register-Guard, May 30, 1983

ANTHONY Lewis commented recently on the "astonishing" and "coold-blooded" way in which the Reagan administration disregards laws. he mentions environmental law, the right to travel, and peacetime censorship as examples. I had been thinking more in terms of his unconstitutionally fighting undeclared wars and violating treaties, but I appreciated Lewis' comments anyway; there are so many examples, one column or one letter isn't sufficient even to name them.

Another journalist recently said it would be nice if Congress would "speak out." That was a good idea, too, but in fact some congressmen did speak out not long ago, and threatened to stop the illegal war in Nicaragua. But the President told them to go ahead, pass "irresponsible" laws if they wanted, but the fighting would go on.

A member of his Cabinet gave a speech which was described as a "call for revolution" against out government because it is controlled by "the religious left." On this point, I'm not clear—has the revolution against constitutional government already taken palce, or is it in progress? Is there more defiance of the Constitution and of Congress and of treaties still to come?

After speaking with Reagan recently, helen Caldicott wonders "if we can make it for the next year and a half until the 1984 elections without a nuclear war." Maybe that's why no one in Congress is talking about impeachment; maybe they are just holding their breath, not wanting to rile the President. Maybe we should all hold out breath until January 1985.

Political Science of Sciences

The Blake List, Volume 1999, Issue 11, February 26, 1999

MAYBE the political right, the Nazis, etc., are the only ones who take art seriously, and can see that it is political work of the most effective sort. Science, when it is approached in the same way, is Art and Politics, and participates in intellectual war.

Acadamic obtuseness has always made it possible to ignore ironic and dialectical language, so I suspect that Ralph Dumain's riddles won't ignite many mental fires.

> The wretched state of the Arts in this Country & in Europe originating
>
> in the Wretched State of Political Science which is the Science of Sciences
>
> Demands a firm & determinate conduct on the part of Artists
>
> to Resist the Contemptible Counter Arts
>
> ...Strength to form the golden armour of science
>
> For intellectual War The war of swords departed now
>
> Are not Religion & Politics the same thing? Brotherhood is religion.
>
> Good & Evil are Riches & Poverty, a Tree of Misery,
>
> propagating Generation and Death.
>
> A Poet a Painter a Musician an Architect:
>
> the Man Or Woman who is not one of these is not a Christian.
>
> The Unproductive Man is not a Christian, much less the Destroyer.

You must leave Fathers & Mothers & Houses & Lands

if they stand in the way of Art.

Prayer is the study of Art.

Praise is the Practice of Art.

Fasting &c., all relate to Art.

The outward Ceremony is Antichrist.

Without Unceasing Practice nothing can be done.

Practice is Art. If you leave off you are Lost.

Jesus & his Apostles & Disciples were all Artists.

Their Works were destroy'd by the Seven Angels

of the Seven Churches in Asia, Antichrist Science.

The Old & New Testaments are the Great Code of Art.

The Whole Business of Man Is The Arts, & All Things Common.

No Secresy in Art.

Christianity is Art & not Money. Money is its Curse.

From a previous post:

I don't think anybody is playing arbitrary games with definitions or willfully stretching the definition of the political beyond recognition. Notice your key word above, "working", (my emphasis added): the implication seems to be that working is acting, engaging in overt political activity, not writing. But Blake was a writer and artist, who took definite positions as a writer if not as an activist on issues of hunger, poverty, tyranny, imperialism, slavery, and much more besides. How you could

interpret this as indifferent to improvement of the human condition in the material world is beyond me.

This is where a productive discussion should begin, rather than end. I hope I am not remembering something different than you are, but what comes to mind is the question of Blake's attitude towards the literal: is the sun a flaming disc that looks like the size of a guinea or the heavenly host screeching holy holy holy? Such symbolic acts of defiance of material reality have yet to be properly analyzed by anyone on this list, including me, esp. in conjunction with some more down-to-earth statements such as "we eat little we drink less/this earth breeds not our happiness." There is an issue of psychological resistance to material conditions in the face of which one is powerless, but these gestures of psychological resistance, that come from real, material, palpable suffering and the will to endure, cannot be reduced to New Age suburbanite hippy-dippy drivel that changing your interpretation changes what's happening, tiptoeing through the tulips as if one gets a free ride to live in a fantasy world.

I would be interested to know whether the scholarly Blake literature addresses all these questions, because I've not seen any that has to date. Rather than continue explicating my own views, let me pose a series of riddles to advance the discussion onto the next level:

(1) How are we to analyze Blake's statements of resistance in defiance of material conditions?

(2) How are we to analyze the political claims of Blake's vague and symbolic descriptions of apocalyptic conditions which somehow result in redemption, the new Jerusalem, in the light of how social change takes place and was taking place in front of Blake's eyes?

(3) When Blake says it was a mistake for Jesus to get involved in politics, and otherwise excuse his own disengagements from the political realm (including the statement Tim cites about how an educated citizenry would be immune to tyranny, and the statement that creation burns up when people cease to behold it), what kind of claim is actually being made? Is Blake advocating that everybody is wasting their time trying to change the political, material conditions of their lives, or merely that prophets like Jesus and himself are ill-advised to get mixed up in potentially life-threatening political situations in which they cannot possibly win?

By pursuing questions such as these, which all follow a similar pattern, I think we can progress much further through this murky character of Blake; symbolic politics relates to material societal conditions.

Re: Biblical Sources and More

The Blake List, Volume 1999, Issue 17, March 4, 1999

In his time (as in the present time), terrible things were used as medications, and probably were more deadly than what they were supposed to cure. Paracelsus invented a magical approach to medicine, in which the official medical crap would be applied to the sword that made the wound, leaving the lucky patient unmedicated. When I used to teach naturopathic physicians, they generally didn't appreciate my suggestion that this principle could account for the relative success of homeopathy when compared with 20th century medicine.

The great biochemist, Albert Szent-Gyorgyi, used to observe that humor was closely allied with the perception of important truth. I think Blake's humor is generally under-appreciated.

From a previous post:

> Beyond being a mere "alchemist", am I wrong in thinking that Paracelsus could also be called a doctor and chemist, who rejected traditional education and medicine, anticipated homeopathy, had something to say about "miner's disease", and could be viewed as a pioneer in both chemical medicine as well as empirical psychological science?

Re: For Raymond Peat

The Blake List, Volume 1999, Issue 15, March 1, 1999

I think the ramifications of that insight are very far-reaching and important. It's hard for many intellectual types to see that whole idea-complexes, as well as particular words, can be "used" creatively or for oppression and manipulation.

> *From a previous post:*
>
> > And was Blake as much of a "Christian" as much as *used* the religion that his country-men and women understood, and which also happened to be conquering the world, for more subversive themes, himself?

The reason I jumped from Blake to Lenin is that I think Marx was only abstract and sketchy in the way he revealed the theological idealism hidden in the various philosophies, but Lenin in his notebooks prophetically and concretely showed the fallacies that were repeated endlessly in 20th century philosophies of science, positivism, language philosophy, etc. Either people don't read Lenin's philosophical work, or they are so trapped in their theologies of "pure science" and other abstract systems that they can't respond in any way to his powerful analysis. I think that's why people don't talk about Blake's highly analytical revelations of the philosophical self-contradictions of the big-shots, it's the deep neokantianism that rules the official mental life at present.

As a biologist, I think Blake "used" the images of "a world all alive" as a fiendishly clever way to by-pass the dogmatic abstractions that ruled philosophy then as now. I think this philosophical condition accounts for the horrifying oppression that "vitalism" and "Lamarckism" have suffered. With Vernadsky and Hoyle, et al., I am inclined to believe that at least in an abstract and general sense, the universe is alive, but the "use" that Blake made of that idea was, I think, possibly the most intelligent philosophical act ever.

Re: Organs of Perception

The Blake List, Volume 1999, Issue 17, March 4, 1999

SINCE I see Blake as one of the few people who saw clearly in the 18th century, I like to look for people in this century who worked constructively with the same themes. Maurice Merleau-Ponty's work with the phenomenology of perception, building on the work of people like Kurt Goldstein, elaborates in modern terms this distinction between passive and active seeing and knowing. From Blake's references and images, I have guessed that Swedenborg's scientific discoveries were being discussed by scientific dissenters in London in Blake's time. The ratio of Blake to Swedenborg would be somewhat equivalent to that of Merleau-Ponty to Sechenov.

From a previous post:

> The phenomenal world is called by Blake "generation" or the "natural," and what he calls "mental" (because it is related to experience by the mind) is what we would call spiritual. The former kind of world is perceived with the "organs of sense" or the "natural and bodily organs," the latter kind with the "imaginative and immortal organs" (DC: The Bard, from Gray K576). I believe that in order to follow Blake one has to take seriously the existence of these "imaginative and immortal organs." This places him squarely in the tradition of Boehme, Swedenborg, etc.
>
> In his tractate NNR(#2) his first statement is: "Man's perceptions are not bounded by organs of perception; he perceives more than sense (tho' ever so acute) can discover."
>
> When Blake says: "the outward Creation . . . is as the Dirt upon my feet, No part of Me" (VLJ), he does not deny its presence (he calls it a "hindrance," and says: "while we are in the world of Mortality we must Suffer" (VLJ)) - but simply emphasizes that he is directed towards the spiritual, which to him is the substantial life.
>
> When Swedenborg writes: "Appearances are the first Things from which the human Mind forms its Understanding, and it cannot shake them off but by an Investigation of the Cause, and if the Cause is very deep, it cannot investigate it, without keeping the Understanding some Time in spiritual Light ...," Blake makes the annotation: "This Man can do while in the body." Blake's outlook is based on this belief that man has the ability to discern more than his bodily senses allow.
>
> At the Creation, the originally infinite organs of man were "shrunk" (into "female space"), and will be expanded when redemption comes,

to again behold Infinity. Our senses can only perceive what they have been structured to perceive, or as Blake puts it: "If Perceptive Organs vary, Objects of Perception seem to vary."

In M26 he says: "Every Natural Effect has a Spiritual Cause."

Re: Organs of Perception

The Blake List, Volume 1999, Issue 17, March 4, 1999

AROUND 1860, Sechenov formulated in a detailed way the idea that the brain and consciousness operate on the basis of reflexes (though Swedenborg seems to have anticipated the whole idea of the cortex of the brain and its (nerve cell) elements as the seat of consciousness with its varied faculties; all apparently for overcoming the dualism of Descartes). And then Merleau-Ponty showed why we shouldn't even believe in the literal reality of reflexes. (P.K. Anokhin worked out the more detailed and modern reasons for rejecting the simplistic idea of "the reflex arc," almost literally expressing the idea that we see, actively, through the eyes, not passively "with" them.) In the Russian tradition, the active consciousness has been taken seriously, unlike those in the west, who with Eccles, have insisted on separating the body from the (soul or) mind. One of my professors of neurology, for example, used to sarcastically ask me which I was going to study, the brain or the mind; he thought Pavlov had rejected the thought that neurologists could study the mind.

From a previous post:

> The ratio of Blake to Swedenborg would be somewhat equivalent to that of Merleau-Ponty to Sechenov.
>
> This makes me interested in looking into Merleau-Ponty, whom I have not read. Perhaps you could identify Sechenov for those of us unfamiliar with his name.

Re: Tim's Definition

The Blake List, Volume 1999, Issue 15, March 1, 1999

I don't discount the historical context of religious dissent at all. Blake would be largely unintelligible without that context. But I think it involves a lot more than "opening a history book" to find historical "facts." I was stating my opinion, not giving an argument. I think the argument first has to make sure that there is a clear understanding of what the big-shot or "official" philosophers were claiming, and then to see how the concepts of the culture of religious dissent could be used to show the internal contradictions in those philosophies. The religious dissenters were concerned narrowly with those churchy issues, Blake wasn't. But since two large contexts are needed before an argument can be made regarding what Blake meant when he talked about Substance and Qualities and Negation and contradiction, I think it's appropriate just to say that I don't think Blake was idiotic enough to have made merely literal use of the vocabulary of religious dissent.

From a previous post:

> I think the historical approach to Blake's diction resolves the paradoxes in favor of Ralph Dumain's suggested interpretation.
>
> This may be your opinion, but how can you possibly argue this on the basis of one quote and no context? I don't think even Ralph, who is an extraordinarily perceptive critic and a very gifted writer, has managed to do anything but list the paradoxes. You refuse even to consider the historical context of religious dissent may have been a factor! The "airhead's" (as opposed to what I might term the "windbags" on the other side of the argument) would have a completely different interpretation of your quote below as having a spiritual connotation, presumably claiming it as an attack on the corruption of worldly religion. I would add the the "reasoning power" (rationalism) is something that Blake clearly rails against, but is a major factor in promoting the radical politics of the era.

Re: Tim's Herring

The Blake List, Volume 1999, Issue 13, February 28, 1999

My recent comment about the political right wing taking art seriously was made in response to the people who are currently trying to separate art from politics, and who would like to limit Blake's political consciousness to religious issues. My remark was topical, but the principle I referred to was broadly historical. Blake appeared to be perfectly conscious of the ways in which not just official censorship, but access to the official exhibitions, and the official promulgation of styles in all the arts, supported the Evil Empire, and oppressed people like him. The tastes of the rich and the ruling classes were met by some painters who collaborated in the destruction of art. After Blake, I don't know of anyone until David Alfaro Siqueiros who so clearly understood the ways in which Money and Empire intervened in art.

From a previous post:

> By the way, the statement about right wing governments and art is a red herring and is very "20th Century centric". Fear of art is only really an issue in societies with some sort of mass media which can use art to spread ideas. Blake lacked anything like this, and in any case many of his target clients were aristocratic patrons! In any case, symbolic and satiric attacks against the establishment were fairly common in the Regency era, and broadly tolerated. More explicit sedition was another thing altogether.

Although Blake used the vocabulary of the religious dissenters, one of his great contributions to culture was his understanding that the bad theologies, and their rationalist definition of matter, had been incorporated into the enlightenment empiricisms and the natural philosophies and sciences. Before Lenin, I don't think there was anyone who perceived the rationalism that was hidden in the crude materialism of the sciences.

I wish that those who would Spiritualize Blake would discuss the term "Nobodaddy," and explain how it fits into a dematerialized world.

To Nobodaddy

Why art thou silent & invisible

The Arts & Sciences are the Destruction of Tyrannies or Bad

Governments Why should A Good Government endeavour to Depress

What is its Chief & only Support

...art and science is fabricated for the purpose of destroying art.

It is the Greatest of Crimes to Depress True Art & Science

The Foundation of Empire is Art & Science...

...& obedient to Noblemens Opinions in Art & Science.

From a previous post:

> I'm not sure of what you mean by your terse statements nor how they address Ralph's questions. Likewise, I'm not sure how you are applying these Blakean Proverbs to your response.
>
> Ralph may often be guilty of being disrespectful, or even vulgar—and someone else's attitudes are simply no excuse for bad writing. But none can dispute that he consistently comes up with some extremely difficult and intriguing questions.

Disrespect and vulgarity aren't necessarily out of place in discussing Blake.

Blake's was the most coherent criticism of the terrible theology hiding within the "Enlightened" philosophies of Hume, Newton, Berkeley, that were in service to empire and commerce.

My point, and Blake's, was that the ruling class knows what it's doing when it controls art and science and philosophy, and art is exactly where political opposition makes its best contribution. My suggestion is that, at present, there isn't much artistic opposition to the New World Order, which is just old-fashioned Empire at its culmination.

I don't know what political application of art might be, application would imply a separation, like a "fund-raising benefit."

I don't know what theoretical statements you refer to. Do you mean about intellectual war? Since Blake tried to develop the idea extensively,

that's where the exactitude could be sought. The references in his works to the philosophical categories that had governmental support in the 18th century make it clear that they are the enemy in his mental war. For me, mental war involves exposing the malevolent and stupid assumptions that impose themselves through the operation of the big sciences, for the benefit of the ruling classes.

Re: Tim's Herring

The Blake List, Volume 1999, Issue 14, March 1, 1999

We might have read the same books, but when I read things by 18th century Tory Gentlemen I try to understand how it was possible to achieve such a uniformly insipid tone of self-righteousness. The academic commentators on art who write that "the true destruction of art" was caused by capitalism are, as far as I have been acquainted with them, trying to imbue themselves with something of the nobility of the earlier ruling classes. Good art was sometimes produced under the catholic church, and that fact is sometimes used to try to separate the "aesthetic" from the "political," though I think it provides more evidence of their linkage. The ideology is heavy in "their motivation was aesthetic, not in any sense political," though it's the ideology that likes to say "I don't have any ideology." Like the academic types who have asserted that "there are no classes in the United States."

From a previous post:

> Blake appeared to be perfectly conscious of the ways in which not just official censorship, but access to the official exhibitions, and the official promulgation of styles in all the arts, supported the Evil Empire, and oppressed people like him.
>
> This sounds rather like uninformed reading from the hymn sheet to me. Anyone who takes the time to look at 18th and early 19th Century political cartoons will realise how little practical censorship existed in the arts. Furthermore, it is a little unfair on institutions like the Royal Academy, who provided free training for artists on the basis of their talent alone. It is true that the hangers at RA exhibitions effectively created trends in artistic taste, but they were taken from amongst the artists themselves, and their motivation was aesthetic, not in any sense political (Blake certainly was represented at the RA from time to time). Incidentally, from the 1850s, the function or arbitor of taste was pretty much ceded to (capitalist) dealers, who in fact still do it, and art has become almost wholly commerce as a result.
>
> In what sense was art destroyed? I'd argue that the plein air naturalism of the early 1800s was in fact a renewal of art, springing from the traditions of Poussin and Gainsborough, and the true destruction of art did not take place until well after Blake's death, when the industrial revolution had created an affluent middle class who wished for decorative

> and sentimentally accesible objects for their front parlours. But then I suspect you read different books than me.

I suppose some people have been impressed by Macauley's "English literature was emancipated forever" by the disappearance of the Licensing Act, but I have never seen any reason to believe that tyrannies take their own laws very seriously. Preventive censorship was replaced by punitive censorship.

In the United States, which hasn't had any Licensing Acts, censorship has been rampant. For example, a college catalog with Blake's Glad Day on the cover, was embargoed by the post office, and couldn't be distributed until language in the text had been deleted.

Do you suggest that Blake was having paranoid delusions when he spoke of the forces that destroy art?

Re: Tim's Herring

The Blake List, Volume 1999, Issue 16, March 1–2, 1999

SINCE I will assume that you have led a remarkably sheltered existence, or else are very young, and so might not be representative of the people in the Blake discussion, I will answer this privately.

I spent many years as a graduate student in several humanities departments of several universities, before I decided that in this country only the sciences tolerate anything like rational dialog. In English, philosophy, linguistics, art history, uniformly the professors mouthed that moronic party line, "there are no classes in the United States," and my fellow students were if anything even more strident. Later, I had friends in departments of sociology who used elaborate rationalizations to justify the same assertions. The sociological literature is full of their crap; the reaction to G. William Domhoff's work was essentially one of hysterical denial. One of the variations on the theme extends into psychology and biology, arguing that since everyone has the same opportunity in this classless society, social differences are really just a natural expression of innate inferiority and superiority. For my entertainment, I would occasionally insert into my seminar papers things that could be taken as defense of such elitism, and these were always the occasion for glowing approval by the asshole professors.

The cover of Emanations from Blake College was enclosed as first class mail, and it was therefore inappropriate for the postmaster to open it, but the image, faintly detected through the envelope, was apparently an excuse to examine the contents of the book. The text that was forbidden was by Gregory Corso, a dialog with Alan Ginsberg. The postmaster, a Republican, was nevertheless a kind man, who returned the 300 copies to me for correction, rather than destroying them. I mentioned that, not because it was unusual as an illegal act of censorship, but because the Blake engraving was the trigger. Two of my uncles were postmasters, so I heard inside stories of postal service behavior, but the periodicals of the 20th century give many more famous examples.

From a previous post:

> I do have, however, two questions prompted by some nearly incomprehensible parts of Mr. Peat's recent post—first: please cite some "academic types" who claim that the USA is a classless society???? I have

read a good deal of commentary on American history and culture, and the notion that it is a common or even an occasional *academic* point of view that US is a classless society comes as a considerable surprise to me. On the contrary, it is usually *academics* who cry in the wilderness against the "common wisdom" that the USA is "classless."

Second: please clarify the event cited with reference to the college catalogue with "Glad Day" on the cover????? The Postal Service "embargoed" it until "the language of the text inside" was altered? This is truly incomprehensible. Why would the presence of a picture on the cover require the alteration of the text inside? How would that solve any problem? Presumably, the "embargo," assuming it ever occurred and is not an example of a foaf tale, would have been caused by the exposed male genitalia on the cover, not by text inside. Very odd narrative, but possible as a form of urban belief legend.

Tim's Aristocrats

The Blake List, Volume 1999, Issue 16, March 1–2, 1999

WRITING and other mental works provide windows into the times and situations of their creators, and I consider Blake to be the best window into the 18th century. If preserving the arts and sciences, the accumulated wisdom of the ages, is very important, then I think it is useful to assume that Blake wasn't in a delusional state when he ranted or grumbled about the class that destroys art and knowledge, and to give serious consideration to what he meant.

"…most informed observers"—is that still an accepted rhetorical device in academic discussion?

Altruistic English aristocratic patrons of the 18th century, I recognize the concept, but to accept it as an important fact seems to be giving too much weight to their own testimony and judgment.

In our century, the commercial forces that you suggested were harmful to art, have more resources than ever before to manipulate tastes. Publishing, academic endowments and direct manipulation of state institutions are used to validate their preferred interpretive frameworks, and ultimately the judgments that are made about history, literature, science, and painting, have to be made in this extremely polluted atmosphere. That's why I think it's important to see Blake's remarks on the destruction of art in a sense more general, and less subjective, than just the issue of blurring painted forms.

From a previous post:

> Do you suggest that Blake was having paranoid delusions when he spoke of the forces that destroy art?
>
> This is certainly a possibility.
>
> However, what Blake meant by the "destruction of art" was the blurring or removal of the "bounding line", a tendency to employ chiaroscuro, admiration for the Flemish masters, and the movement towards naturalistic realism in landscape (all of which, incidentally, were characteristics of the work of John Linnell at the time he and Blake were close friends, so clearly Blake did not feel all that strongly about it). This is not "destruction" in anything other than a highly personal and subjective sense.
>
> In actual fact, I would venture to suggest that most informed observers would say that the first twenty or thirty years of the last century was one of the better periods for English art. Where things did drift into

crass and sickly sentimentality and "production line" art was when the dealers got involved and the whole exercise became commercial, leading to the great art boom in the late 1800s. Furthermore, dealers put great pressure on the hangers at the RA and other exhibitions to favour artists they represented.

On the other hand, aristocratic patrons viewed their contribution to art as somewhat altruistic, and tended not to interfere with the artist's work. The hangers at exhibitions were taken from among the artists themselves and were more or less in tune with the direction their fellows wished to go, within certain parameters of conventional taste (which are inevitable). Although not perfect, this was a fundamentally much more healthy situation for the development of art than the dealer led commercialization.

Tim's Definition

The Blake List, Volume 1999, Issue 13, February 28, 1999

I think Tim's argument is doing an injustice to history, as much as to Blake. If Blake used the vocabulary of 18th century songs of religious dissent in attacking State and Class oppression, and therefore was spiritual rather than political, then the people who sang christian hymns while marching in the streets of the United States were primarily interested in religion, and the communists among them were for the moment no longer political revolutionists. That's no way to argue.

From a previous post:

> So the quote above is not political, except in the sense that opposition to a political entity is a political act,

To me, this is an astounding statement. Does it suggest that the writings of Marx and Engels in themselves weren't unqualifiedly political?

From a previous post:

> But in view of the fact he did nothing tangible to promote or implement his views, one has to say that if he was a political writer, he failed.

Don't most political writers fail? What's the point? Can you comfortably and historically assert that Blake did "nothing tangible to implement his views"? Are political pamphlets political only if they lead to revolutions?

From a previous post:

> I can only assume that the misinterpretation of a quote with a clear and blindingly obvious religious dissenting content is based on ignorance of the history of religious dissent, His adoption in our times is not because he has anything particularly new to say, but because he had the good fortune to have written a few things which had resonance with post war student politics, he appears to advocate free love

Why is your interpretation of a certain passage blindingly obvious, while you frame his advocacy of free love as an appearance? Robinson thought Blake's advocacy was embarrassingly blatant.

From a previous post:

> In any case, I think the answers to Ralph's questions are simple. He raises paradoxes based on his assumption that Blake used symbolic constructs to frame his political ideology and in fact had no spiritual objectives. The fact of the matter is that Blake actually believed what he said to have literal truth. If you apply this idea to what he said, even if you don't agree with him, the paradoxes vanish.

I think the historical approach to Blake's diction resolves the paradoxes in favor of Ralph Dumain's suggested interpretation.

> And this is the manner of the Sons of Albion in their strength
>
> They take the Two Contraries which are calld Qualities, with which
>
> Every Substance is clothed, they name them Good & Evil
>
> From them they make an Abstract, which is a Negation
>
> Not only of the Substance from which it is derived
>
> A murderer of its own Body: but also a murderer
>
> Of every Divine Member: it is the Reasoning Power
>
> An Abstract objecting power, that Negatives every thing
>
> This is the Spectre of Man: the Holy Reasoning Power
>
> And in its Holiness is closed the Abomination of Desolation
>
> Tell them to obey their Humanities, & not pretend Holiness;
>
> When they are murderers: as far as my Hammer & Anvil permit
>
> Go, tell them that the Worship of God, is honouring his gifts
>
> In other men: & loving the greatest men best, each according

To his Genius: which is the Holy Ghost in Man; there is no other

God, than that God who is the intellectual fountain of Humanity;

Pharmaceutical Compositions Containing Dehydroepiandrosterone and Other Anesthetic Steroids in the Treatment of Arthritis and Other Joint Disabilities

United States Patent, December, 1986

Background of the Invention

This invention is concerned with compositions and methods of treating rheumatoid arthritis, osteoarthritis, and arthritis associated with psoriasis and with lupus and other auto-immune diseases, and also for treating non-specific joint pain associated with stress or incidental to another ailment, using dehydroepiandrosterone (DHEA) and/or other anesthetic steroids dissolved in an oily vehicle, and preferably administered topically or orally.

The extensive use of cortisone and related anti-inflammatory steroids in treating arthritis has been limited by the knowledge of several side effects, including calcium loss and osteoporosis, immune suppression, and atrophy of various tissues, including the adrenal glands. Nonsteroidal anti-inflammatory agents have been used with some success to avoid the glucocorticoids' side effects, but generally are ineffective in preventing the advance of the disease process. Other agents have been used or proposed which retard the advance of the disease, possibly by inhibiting mitosis, but they generally have toxic side effects.

It would be desirable to use in treatment substances which are normally present in the body at high levels, since these normal substances, especially when used in physiological quantities, rarely have harmful side effects.

The improvement which sometimes occurs during pregnancy in women suffering from arthritis has led to the experimental use of some of the hormones of pregnancy in treating arthritis, but the female sex hormones would obviously produce side effects when used in large doses in males.

Some steroidal substances, however, lack conventional hormonal activity and are normally present in significant amounts in both males and females. A number of such steroids, e.g. dehydroepiandrosterone, are present

in elevated quantities during pregnancy. Such steroids have received little attention since they have been considered to be only chemical intermediates or end products destined for nothing more important than to be excreted. It was therefore surprising to find that a number of these substances are useful in the treatment of arthritis and related diseases.

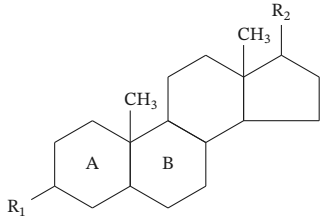
It is an object of this invention to provide an anti-inflammatory pharmaceutical preparation useful for the treatment of arthritis and lacking undesirable hormonal side effects. It is a further object of this invention to provide such a pharmaceutical preparation in a form suitable for administration locally to the affected joints without requiring injection.

Summary of the Invention

The present invention is concerned with compositions and methods of treating rheumatoid arthritis, osteo-arthritis, and arthritis associated with psoriasis and with lupus and other auto-immune diseases, and also for treating non-specific joint pain associated with stress or incidental to another ailment, using dehydroepiandrosterone and/or other anesthetic steroids dissolved in an oily vehicle, and preferably administered topically or orally.

Detailed Description of the Preferred Embodiments

Arthritis, including rheumatoid arthritis, osteo-arthritis and arthritis associated with psoriasis and with lupus, as well as other auto-immune diseases, and non-specific joint pain associated with stress or incidental to another ailment, may be successfully treated by administering to a subject in need of such treatment, including a human patient, an effective amount of an anesthetic steroid, preferably a natural anesthetic steroid having 19 or 21 carbons, more preferably selected from compounds of the formula:



wherein R_1 is O or OH and R_2 is O, OH, or $COCH_3$; and which may contain one double bond in ring A and/or ring B.

Examples of such compounds are dehydroepiandrosterone (DHEA), iso-androsterone, etiocholanolone, progesterone, and pregnenolone.

Combinations of such steroids may be used. When the patient being treated is male, combinations containing testosterone are preferably used.

Compounds considered to be equivalent to the foregoing and also falling within the scope of this invention are steroids of the above-depicted structure having H, methyl, fluorine, or chlorine substituents, as well as easily hydrolyzable esters of all the foregoing.

Suitable pharmaceutical compositions for use according to this invention comprise at least one of the above-described compounds, together with suitable pharmaceutical carriers and/or diluents, preferably the carriers specified in the preferred embodiments described below. In such pharmaceutical compositions, the proportion of therapeutically active to carrier substance can vary between about 1 % to 99 % by weight. The compositions can be prepared in various pharmaceutical forms, such as granules, tablets, pills, suppositories, capsules, suspensions, salves, lotions, and the like. Pharmaceutical organic or inorganic carriers and/or diluents suitable for oral and topical use can be used to make up compositions containing the therapeutically active compounds. Diluents known to the art include vegetable and animal oils and fats. Stabilizing agents, wetting and emulsifying agents, salts for varying the osmotic pressure or buffers for securing an adequate pH value, and skin penetration enhancers can be used as auxiliary agents. The compositions may further contain other therapeutically active compounds, e.g. selected from the group of drugs commonly used in the treatment of arthritis.

For oral use, the pharmaceutical composition of the invention appropriately contains from about 10 % to 100 % by weight of the active material. For topical use, the composition appropriately contains from about 1 % to 15 % by weight of the active material.

Generally for oral use it is preferred that the active ingredients in dry form be mixed with tocopherol to form a paste for capsuling. For topical use, solubilization in tocopherol and olive oil is preferred.

A preferred composition for oral use comprises about 10 mg of the active material, preferably DHEA, about 50 mg pregnenolone, about 5 mg progesterone in 1200 mg tocopherol.

A preferred composition for topical use comprises 5 % of the active material, preferably DHEA, 80 % mixed tocopherols, and optimally up to 10 % olive oil and up to 3 % progesterone. Testosterone up to about 0.5 % may also be added.

The dosage required may vary from about 10 mg to 200 mg active material orally, or 400 mg to 1000 mg active material topically, and may be repeated twice per day.

Generally, for oral administration, a single dosage of about 10 mg to 50 mg of therapeutically active compound in an appropriate carrier is effective. For topical use, a preparation containing about 8 % of therapeutically active compound should be spread in a single application on the skin over the painful area in an amount of between about 0.05 mL to 0.2 mL per square inch of skin. The preparation should be thoroughly rubbed in, and the area covered to avoid rubbing away of the compound before absorption. Warmth may be applied locally to speed absorption.

The invention will be further described in the following examples which are not to be construed as limiting the invention.

Example 1

Combined were 100 mg of micropulverized pregnenolone with 100 mg of 10 % DHEA in tocopherol to form a paste which was capsuled for oral use.

Example 2

For oral use, 100 mg of micropulverized pregnenolone was combined with 50 mg of 10 % DHEA and 50 mg of 10 % progesterone to form a paste which was capsuled.

Example 3

For topical use, a mixture containing 72 % tocopherol, 20 % olive oil, 5 % DHEA, 2.85 % progesterone, and 0.15 % testosterone was prepared by stirring the steroids into the tocopherol until dissolved, then adding the olive oil.

Example 4

The following case histories illustrate the effectiveness of the compositions of this invention in treating arthritis and joint pain:

Case 1. A 78 year old man. He was considered to have mild osteo-arthritis, mainly in his knees. For a few years he had found it increasingly difficult and painful to rise after sitting and to walk. He coated each knee and the immediately adjoining area with a solution containing 2.5 % dehydroepiandrosterone and 2.5 % progesterone in a solvent consisting of equal amounts of mixed tocopherols and olive oil, and remained sitting for two hours. He rose easily, walked without pain, and his knees

remained comfortable without another application of the solution. A week later he applied a 3% solution of dehydroepiandrosterone to his hands, and reported elimination of pain and increased flexibility within an hour. He has remained free of symptoms for eight months with continued treatment.

Case 2. A 72 year old woman. She was considered to have mild rheumatoid arthritis which was degenerating into osteo-arthritis, with her fingers being the most seriously affected joints. A 3% solution of dehydroepiandrosterone in olive oil was applied to one index finger, and a 10% solution of progesterone in mixed tocopherols was applied to the other index finger. All of her fingers had been rigid for over a year, with the result that she was extremely disabled. Forty minutes after the dehydroepiandrosterone solution had been applied, the finger treated with the composition containing dehydroepiandrosterone could be bent enough to touch the base of her thumb, without significant pain, but none of her other fingers showed any improvement. Several days later, the dehydroepiandrosterone solution was applied to all of her fingers, with similar good results. After about 6 months, stiffness and pain returned in spite of use of DHEA, and progesterone added to the treatment caused continued improvement.

Case 3. A 60 year old woman with a long history of rheumatoid arthritis and with serious degeneration of many joints. She had undergone surgery several times, for implantation of two artificial joints and for repair of joint cartilage. She walked as little as possible, and experienced pain, inflammation and fatigue from excessive walking. She applied a solution containing 7% dehydroepiandrosterone and 3% progesterone in solvent consisting of tocopherol, 90%, and olive oil, 10%. She applied the solution several times one afternoon and the next morning to all affected joints, including hands, wrists, elbows, knees, and ankles. She experienced what she said was complete relief, and spent the next two days walking around the town sightseeing, without any of the after-effects she had previously experienced from walking.

Case 4. A 61 year old man with mild, unclassified arthritis of the thumb and fingers of his right hand, which prevented him from playing golf, but was otherwise not seriously disabling. A solution essentially identical to that used in Case 3 was rubbed into the painful joints. In less than fifteen minutes he said that all the pain was gone, even with pressure and movement.

Case 5. A 62 year old man. His knees had been stiff, painful, and inflamed for over two years, following an accidental fall onto his knees. Arthroscopic examination revealed damaged cartilage in his right knee, and surgery was recommended to restore function. The patient refused surgery, even though he walked with difficulty and had to use his left leg, which was also affected, to lift himself slowly up steps. He said he had not slept well since he had developed the arthritis, because the pain woke him repeatedly during the night, and only the use of an analgesic would allow him to go back to sleep. He coated his knees and the skin above and below the knees to a distance of about four inches from the knee, with a total of 20 mL of a solution essentially identical to that used in Case 3. Within 30 min he appeared to be able to walk more normally, and about 45 min after applying the solution he remarked that he believed he was able to walk more easily. He repeated the application that night before going to sleep. Around 10 o'clock the next morning he returned and laughingly demonstrated his knees by running up the stairs, and said that he had been able to sleep through the night for the first time in years, and had not taken his usual analgesic. Topical treatment was discontinued after a few days, and he remained free of symptoms while taking 60 mg of pregnenolone orally, daily.

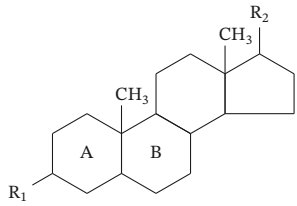
Case 6. A 61 year old woman. Painful and stiff joints in her hands had interfered with her work as a musician, and had made it impossible to sleep through the night, since the pain woke her two or three times during the night. A solution essentially identical to that used in Case 3 was applied to the painful joints early in the evening, and a few hours later she was able to go to sleep without taking analgesic and slept through the night. She occasionally uses the same solution preventively, and has not had a recurrence of the joint pain or stiffness.

Claims

What is claimed is:

1. A method for treating arthritis and joint pain and disability, comprising administering to a patient in need of such treatment a pharmacologically effective dose of dehydroepiandrosterone.

2. A method for treating arthritis, comprising administering to a patient in need of such treatment a pharmacologically effective dose of at least one compound selected from the group of the anesthetic class of naturally occurring steroids of the formula:



wherein R_1 is O or OH and R_2 is O, OH, or $COCH_3$; and which may contain one double bond in ring A and/or ring B.

3. The method of claim 2 in which said steroid is selected from the group consisting of dehydroepiandrosterone, iso-androsterone, etiocholanolone, pregnenolone, and progesterone.

4. The method of claim 2 wherein the compound is administered orally.

5. The method of claim 2 wherein the compound is administered topically.

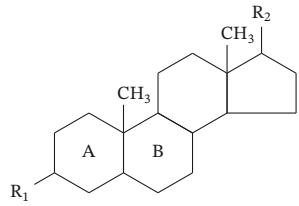
6. The method of claim 2, wherein the arthritis to be treated is osteo-arthritis.

7. The method of claim 2, wherein the arthritis to be treated is rheumatoid arthritis.

8. The method of claim 2, wherein the arthritis to be treated is arthritis associated with auto-immune disease.

9. The method of claim 2, wherein the condition to be treated comprises non-specific joint pain or joint disability resulting from stress.

10. A pharmaceutical composition useful for the treatment of arthritis comprising an effective amount of at least one compound selected from the group consisting of the formula:



wherein R_1 is O or OH and R_2 is O, or OH; and which may contain one double bond in ring A and/or ring B and tocopherol, in a suitable pharmaceutical carrier.

11. The composition of claim 10 in which said steroid is selected from the group consisting of dehydroepiandrosterone, iso-androsterone, and etiocholanolone, in a suitable pharmaceutical carrier.

12. The composition of claim 11 comprising an effective amount of dehydroepiandrosterone and tocopherol.

13. The composition of claim 11 also comprising progesterone.

14. The composition of claim 11 also comprising testosterone.

15. The composition of claim 11 also comprising olive oil.

Treatment of Progesterone Deficiency and Related Conditions With a Stable Composition of Progesterone and Tocopherols

United States Patent, March, 1984

The present invention relates to the composition of a biologically compatible high concentration solution of progesterone in tocopherol, with or without modifying substances, which can be used transdermally, orally, and in suppository and pessary form, for the correction of progesterone deficiency states and other diseases.

Progesterone deficiency can be defined in relation to a norm, and also in relative terms, taking into account the absolute level of progesterone in the tissues and the presence and levels of antagonists to its actions, including estrogens, prolactin, and androgenic steroids, and it can also be defined in the empirical sense, in which symptoms abate when progesterone is administered.

Physicians have long sought an oral and/or transdermal form of progesterone which is stable in high concentration and which is assimilated easily by the body, for use when injectable forms of progesterone are not tolerated. A nontoxic and low-allergenic form is of special value for use in allergic patients, and for all users the absence of a toxic solvent is of obvious value.

Many physicians have used progesterone dissolved in ethanol, but ethanol has a higher mutual solubility with water than with progesterone, causing the bulk of the progesterone to be crystallized out of solution as the alcohol solvent mixes with biological fluids. That composition is ineffective because it fails to deliver progesterone in practical quantities and usable form. Other compositions containing solvents such as benzyl benzoate, benzoyl alcohol or phenol are limited in their applicability because of their toxicity, irritating properties, or allergenicity. Since allergies are common in the condition of progesterone deficiency, it follows that the effectiveness of compositions containing allergenic solvents is limited.

Progesterone has been used medically to treat pregnancy complications, menstrual abnormalities, menopausal difficulties, sev-

eral types of malignant and non-malignant tumors, neurological and psychological symptoms, and many other specific problems. The composition described in this patent can be used effectively for all of the purposes for which progesterone in its older compositions is effective. In addition, the composition described in this patent is useful for several new purposes, including treatment of psoriasis, eczema, senile skin changes including warts, superficial burns, allergies, abnormal hair growth resulting from androgen excess, intestinal inflammation and bowel spasms, migraine, and for promoting maturation of thymus-derived lymphocytes, and as a contraceptive.

It is an object of the present invention to provide a composition and method for the treatment of progesterone deficiency conditions.

It is another object of the present invention to provide such a composition and method which overcome the shortcomings of the prior art.

It is another object of the present invention to provide a composition which does not decompose into solvent and crystallized solute, progesterone, under any presently known conditions of storage or use.

It is another object of the present invention to provide such a composition which is non-toxic and which may be used frequently over long periods without adversely affecting the tissues which it contacts.

It is a further object of the present invention to provide such a composition which is economical and easily used for the prevention and treatment of progesterone deficiency conditions and other diseases.

Still further objects and the entire scope of applicability of the present invention will become apparent from the detailed description and specific examples, but it should be understood that the examples, while indicating preferred embodiments of the invention, are given only for illustration, since changes within the spirit and scope of the invention will become apparent to those skilled in the art from this description.

It has been found that the above objects may be attained by a composition which contains as essential ingredients progesterone and tocopherol. As will be hereinafter explained more fully, the composition may also contain additives for various purposes. The composition may be administered by spreading on the skin, by holding in contact with mucous mem-

branes, or by ingesting, and can be used as frequently as needed.

Suitable forms of tocopherol include d-alpha tocopherol, and mixed tocopherols of the dextro-rotatory form.

Suitable additives include coconut oil, palm kernel oil, jojoba oil, and olive oil, used in concentrations up to about 15 % to lower the viscosity of the solution and to thus speed absorption; ascorbyl palmitate and/or glyceryl monophosphate in concentrations sufficient to emulsify the composition with water; biological or organic gels including aloe gel and extracts from marine algae to thicken the consistency and to stabilize the emulsion; and ethanol, in a concentration of up to about 7 % by volume, to modify consistency and to increase absorption of progesterone.

The composition is prepared by mixing the ingredients to obtain a homogeneous product. Stirring at room temperature is adequate, but may require several days to reach complete homogeneity. An oxygen-free atmosphere is preferred but not essential. If higher temperatures are used for faster mixing, an oxygen-free atmosphere becomes more important to prevent oxidation of the materials.

Progesterone and tocopherol can be mixed in the proportions of from 1 % to 25 % progesterone by weight, to about 75 % to 99 % of tocopherol, with a preferred concentration for most uses of from about 10 % to 20 % progesterone to about 80 % to 90 % tocopherol.

This invention is further described in the following specific examples, which are to be considered only as illustrative of preferred embodiments of the present invention.

Example 1

10 kg of progesterone is added to 90 kg of mixed tocopherols of the dextro-rotatory form, and stirred at a temperature of 45 °C until homogeneous. 35 kg of glyceryl-monostearate is added to the composition and stirred at 45 °C until a homogeneous mixture is produced. This oil phase is then homogenized at 45 °C with a water phase composed of 200 kg of water mixed homogeneously with 5 kg of dry aloe gel, and 1 kg of sorbic acid as a preservative.

The resulting emulsion is then applied to the skin in treating systemic progesterone deficiency, and for treating local skin conditions including psoriasis, or applied to a vaginal diaphragm or pessary or inserted vaginally with an appropriate applicator, for use as a contraceptive or for treating systemic progesterone deficiency.

Example 2

20 kg of progesterone is added to 80 kg of mixed tocopherols, and stirred at a temperature of 40 °C until homogeneous.

The resulting composition is applied to a pessary for use as a contraceptive, or as a local treatment for dysplasia of the uterine cervix, or is administered orally for treatment of a systemic progesterone deficiency. No preservative is needed in this composition.

Example 3

10 kg of progesterone is added to 90 kg of d-alpha tocopherol and stirred at a temperature of 30 °C until homogeneous.

The resulting composition is then encapsulated and administered orally for treatment of systemic progesterone deficiency.

Claims

What is claimed is:

1. A composition consisting essentially of progesterone solubilized in tocopherol.

2. A pharmaceutical composition suitable for administering progesterone to a patient in need thereof, comprising a pharmaceutically effective amount of progesterone solubilized in tocopherol.

3. The composition of claim 2 wherein progesterone is present at a concentration of from about 1 % to 25 % by weight.

4. The composition of claim 2 also containing an emulsifier, water and a preservative.

5. A method for administering progesterone to a patient in need thereof comprising administering to said patient by means other than intravenous injection, a pharmaceutically effective mixture of progesterone solubilized in tocopherol.

6. The method of claim 5 which comprises the oral administration of said mixture.

7. The method of claim 5 which comprises the topical administration of said mixture.

8. The method of claim 5 which comprises placing said mixture in contact with the mucous membranes of the patient.

9. The method of contraception in which a pharmaceutically effective amount of progesterone solubilized in tocopherol is applied to the vaginal membranes and the uterine cervix by means of a vaginal diaphragm, a pessary, or other means of vaginal application in which the composition is retained within the vagina for about four hours or more after each application.

10. A method for making a pharmaceutically effective composition for the administration of progesterone to a patient in need thereof comprising solubilizing progesterone in tocopherol.

Paintings

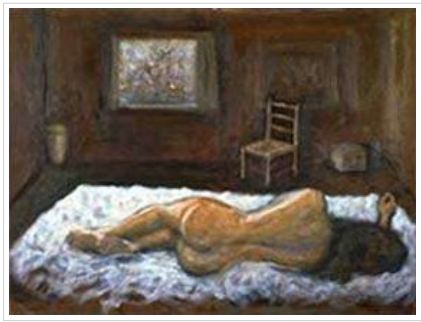
> "I think of myself primarily as a painter who doesn't have any customers."
>
> — Ray Peat

PAINTING and science have been closely associated historically, because both used to involve close, intense examination of their subject, generalization based on experience, and imaginative consideration of the possibilities. That has changed but not because of any intrinsic change in knowledge.

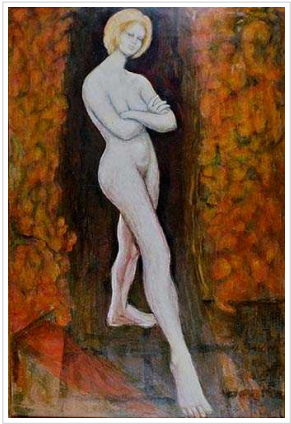
Knowledge always changes through time, but vested interests try to permit only those changes that are good for them. Authoritarian education derives its authority from political and economic power, and generally not from the quality of the knowledge it inculcates. As education became more important economically in the twentieth century, it became more specialized, in the sense that each teacher devoted his full time to an increasingly narrow topic. In this state, the specialist loses his authority when he ventures to evaluate the big picture.

In the 19th century, biologists were usually competent painters, but as specialization took over at the beginning of the 20th century, both science and painting became "abstract." Mathematics came to be called the language of science, and a science was considered to be more scientific when it was more mathematical. The mathematical habit of mind inclines biologists to see organisms as disembodied information, ultimately as the information contained in the genetic code. Change (they are likely to say) is random, "chaotic," ultimately unknowable. There is no place in this system for a radical critic of the purpose and direction of the system.

If physicists and biologists learn to see the world in a lively way by exercising the power to paint, they will learn to prevent the atrophy of their critical powers.

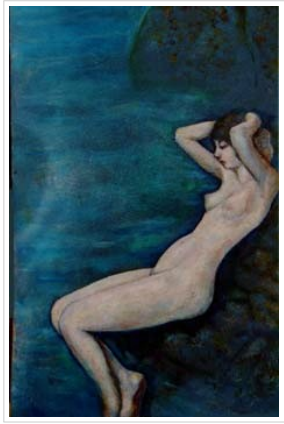




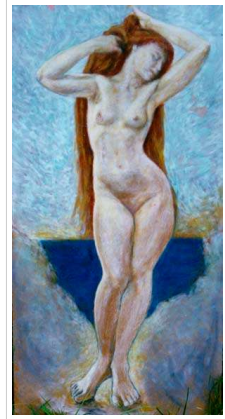




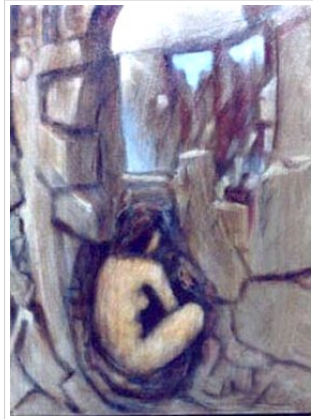




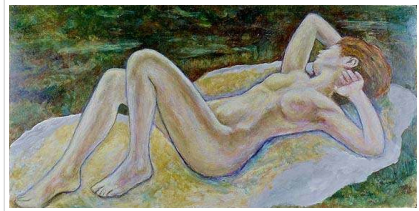




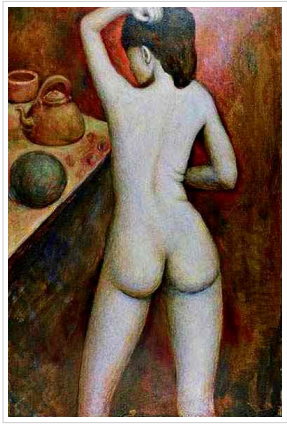








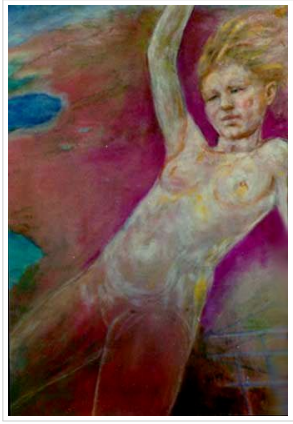












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BSE, Mad Cow, Scrapie, etc.

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Bone Density: First Do No Harm

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Hot Flashes, Energy, and Aging

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Multiple Sclerosis, Protein, Fats, and Progesterone

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RU486, Cancer, Estrogen, and Progesterone

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