The problem of Alzheimer's disease as a clue to immortality

From the original article in 2006. Author: Ray Peat.

Contents

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 grams) is about 50%.greater than at the age of 16-20 (23.04 grams). 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.

M. C. Diamond, Enriching Heredity: The Importance of the Environment on the Anatomy of the Brain. Free Press, N.Y.,

1988. C. Finch and L. Hayflick, Handbook of the Biology of Aging. Van Nostrand Reinhold, N.Y., 1977.

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.

I f 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 (Hershey, "Entropy, basal metabolism and life expectancy," Gerontologia 7, 245-250, 1963) 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 (causing the temperature to fall)--"negative heat production"--but the exact meaning of this isn't clear. (B. C. Abbott, et al., "The positive and negative heat production associated with a nerve impulse," Proc. R. Soc. B 148, 149, 1958; R. D. Keynes and J. M. Ritchie, "The initial heat production of amphibian myelinated nerve fibres," Proc. Physiol. Soc., June 1970, page 29P-30P: "It is now clear that in both crustacean...and mammalian (Howarth, et al., 1968) non-myelinated fibres there is an initial production of heat during (or soon after) the action potential, 80% of which is rapidly reabsorbed.") A. I. Zotin ("Aging and rejuvenation from the standpoint of the thermodynamics of irreversible processes," Priroda, No. 9, 49-55, 1970), 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-Gyorgyi'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

EDUCATION, DIET AND MEDICINE INTERACT

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.)

D. E. Brenner, et al., Postmenopausal estrogen replacement therapy and the risk of Alzheimer's disease: A population-based case-control study," Am. J. Epidemiol. 140, 262-267, 1994. "Women tend to have higher age-specific prevalence and incidence rates of Alzheimer's disease than do men." A.F. Jorm, The Epidemiology of Alzheimer's disease and related

disorders, Chapman and Hall, London, 1990, and W. A. Rocca, et al., Ann. Neurol. 30, 381-190, 1991.

H. C. Liu, et al., "Performance on a dementia screening test in relation to demographic variables--study of 5297 community residents in Taiwan," Arch. Neurol. 51(9), 910-915, 1994. "Commonly used dementia screening tests may be unfair to poorly educated individuals, especially women and rural residents."

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 Ca2+ 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 (Brown and Gordon, Fed. Proc. 29, 684, 1970, and Can. J. Microbiol. 18, 1463, 1972) or immunostimulant which has also been found to have an anti-senility effect (Doty and Gordon, Fed. Proc. 29). Adenosine is a free radical scavenger, and protects against calcium and glutamate excitotoxicity. (I. Yokoi, et al., "Adenosines scavenged hydroxyl radicals and prevented posttraumatic epilepsy," Free Radical Biol. Med. 19(4), 473-479, 1995; M. P. Abbracchio, et al., "Adenosine A(1) receptors in rat brain synaptosomes: Transductional mechanisms, efects on glutamate release, and preservation after metabolic inhibition," Drug Develop. Res. 35(3), 119-129, 1995.) 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 P450 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; see Savolainen, et al., 1994. 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. E. Roberts, Ann. N. Y. Acad. Sci. 396, 165, 1982; B. Reisberg, et al., N. Engl. J. Med. 308, 721, 1983.

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."

T. Fujita, "Calcium, parathyroids and aging," in Calcium-Regulating Hormones. 1. Role in Disease and Aging, H. Morii, editor, Contrib. Nephrol. Basel, Karger, 1991, vol. 90, pp. 206-211.

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 (1975, J. Orthomol. Psychiatry) 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 (J. H. Benington and H. C. Heller, "Restoration of brain energy metabolism as the function of sleep," Progress in Neurobiol. 45, 347-360, 1995) 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. (L. N. Simanovskiy and Zh. A. Chotoyev, "The effect of hypoxia on glycogenolysis and glycolysis rates in the rat brain," Zhurnal Evolyutsionnoy Biokhimii i Fiziologii 6(5), 577-579, 1970.)

J. H. Benington and H. C. Heller, "Restoration of brain energy metabolism as the function of sleep," Prog. in Neurobiology 45, 347-360, 1995. "...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...."

The terms "functional quiescence" and "G0 quiescence" are similar in meaning to the resting state; I think of cells in the state of "G0 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. O. Toussaint, et al., "Cellular aging and energetic factors," Exp. Gerontology 30(1), 1-22, 1995. "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. A. J. Honour, et al., "The effects of changes in diet on lipid levels and platelet thrombus formation in living blood vessels," Br. J. Expt. Pathol. 59(4), 390-394, 1978--corn oil caused platelets to be more sensitive to ADP.

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). (G. S. Roth, et al., 1995.) 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. (L. F. Agnati, et al., "The concept of trophic units in the central nervous system," Prog. in Neurobiol. 46, 561-574, 1995. Any factor producing edema tends to disrupt the extracellular matrix (Chan and Fishman, 1978, 1980, and L. Loeb, 1948.)

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 (Siesjo, et al., 1989). 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 (J. M. Bourre, N. Gozlan-Devillierre, O. Morand, and N. Baumann, "Importance of exogenous saturated fatty acids during brain development and myelination in mice," Ann. Biol. Anim., Biochim., Biophys. 19(1B), 172-180, 1979.

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 (H. Katsuki and S. Okuda, 1995.) 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. (J. Niquet, et al., "Glial reaction after seizure induced hippocampal lesion: Immunohistochemical characterization of proliferating glial cells," J. Neurocytol. 23(10), 641-656, 1994: "...hippocampal astrocytes from kainate-treated rats experess A2B5 immunoreactivity, a marker of type-2 astrocytes." "This suggests that in the CNS, normal resident astrocytes acquire the phenotypic properties of type-2 astrocytes.")

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 over-produced. 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. (A. J. Cross, et al., "Cortical neurochemistry in Alzheimer-type dementia," Chapter 10, pages 153-170 in *Aging of the Brain and Alzheimer's Disease, Prog. in Brain Res. 70, edited by D. F. Swaab, et al., Elsevier, N.Y., 1986.*)

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..

VIII: 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. (T. Henics, "Thoughts over cell biology: A commentary," Physiol. Chem. Phys. & Med. NMR 27, 139-140, 1995.) 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.

References

S. Rose, "Genuine genetics or conceited convenience?" Trends in Neuro. Sci. 17(3), 105, 1994.

F. P. Monnet, et al., "Neurosteroids, via sigma receptors, modulate the [H3]norepinephrine release evoked by N-methyl-D-aspartate in the rat hippocampus," P.N.A.S. (USA) 92(9), 3773-3778, 1995. "...progesterone may act as a sigma antagonist."

J. L. Sanne and K. E. Krueger, "Expression of cytochrome P450 side-chain cleavage enzyme and 3 beta-hydroxysteroid dehydrogenase in the rat central nervous system: A study by polymerase chain reaction and in situ hybridization," J. of Neurochemistry 65(2), 528-536, 1995.

V. V. Zakusov and R. U. Ostrovskaya, "Increased resistance of mice to hypoxia under the influence of tranquilizers of the benzodiazepine series," Byulletan Eksperimentalnoy Biologii i Meditsiny 71(2), 45-47, 1971. [The protection was not from the sedative effects, "Rather, the protective effect of these compounds is attributed to some specific intervention in the metabolism whereby the sensitivity of the tissues to oxygen insufficiency is reduced. ...the cortical structures of the brain especially appear to derive enhanced resistance to oxygen deficiency."]

A. I. Zotin, "Aging and rejuvenation from the standpoint of the thermodynamics of irreversible processes," Priroda 9, 49-55, 1970. [The process of aging "...is manifested by a decrease in entropy and...also by a continuous decrease in the rate of heat production.. The organism exhibits two types of approaches to a steady state: (i) constitutive movement of the system to the final steady state and (ii) inducible return of the system to the current steady state after deviating under the influence of internal or external factors. Oogenesis represents a constitutive deviation from the steady state; entropy reaches a level sufficient for the start of development and passage of the living system into the state of constitutive approach to the final steady state. From the standpoint of the thermodynamic theory of development, oogenesis reflects the process of regeneration of the system. In all other stages of life there is only the aging process accompanied by a decrease in entropy."

M. M. Tikhomirova, et al., "Mechanisms underlying the resistance of genetic material of the animal cell to stress treatment," Genetika 30(8), 1092-1104, 1994. "...these studies prove that the formation of a mutation is a multistage process involving many cell and organism systems...which are affected by environmental factors.... They can hinder or accelerate the mutational process, in this way providing both a superadditive effect and adaptive response. Recent studies deal with a universal system of heat shock proteins, which is involved in the maintenance of resistance of genetic material and genetic processes in the cell." Gross, "Reproductive cycle biochemistry," Fertility & Sterility 12(3), 245-260, 1961. "The maintenance of an environment conducive to anaerobic metabolism--which may involve the maintenance of an adequate supply of the substances that permit anaerobiosis...seems to depend primarily upon the action of estrogen." "Glycolytic metabolism gradually increases throughout the proliferative phases of the cycle, reaching a maximum coincident with the ovulation phase, when estrogen is at a peak. Following this, glycolysis decreases, the respiratory mechanisms being more active during the secretory phase. Eschbach and Negelein showed the metabolism of the infantile mouse uterus to be less anaerobic than that of the adult. If estrogen is administered, however, there is a 98 per cent increase in glycolytic mechanisms.""The effect of the progestational steroids may be such as to interfere with the biochemical pattern required for support of this anaerobic environment."

M. A. G. Sissan, et al., "Effects of low-dose oral contraceptive oestrogen and progestin on lipid peroxidation in rats," J. of International Med. Res. 23(4), 272-278, 1995. "The levels of lipid peroxides, free fatty acids and glutathione in the liver, and of serum ceruloplasmin increased significantly with oestrogen treatment. Lipid peroxides (in the liver only), and serum ceruloplasmin decreased significantly when progestin was administered. The activities of superoxide dismutase and catalase decreased significantly in the oestrogen group...but increased in the progestin group."

A. Jendryczko, et al., "Effects of two low-dose oral contraceptives on erythrocyte superoxide dismutase, catalase and glutathione peroxidase activities," Zentralbl. Gynakol. (Germany) 115(11), 469-472, 1993. "These data suggest that low-dose oral contraceptives, by decreasing the activities of antioxidant enzymes and by enhancing the lipid peroxidation, increase the

risk of cardiovascular disease."

J. W. Olney, "Excitotoxins in foods," Neurotoxicology 15(3), 535-544, 1994. "The most frequently encountered food excitotoxin is glutamate which is commercially added to many foods despite evidence that it can freely penetrate certain brain regions and rapidly destroy neurons by hyperactivating the NMDA subtype of glutamate receptor."

K. Savolainen, et al., "Phosphoinositide second messengers in cholinergic excitotoxicity," Neurotoxicology 15(3), 493-502, 1994. "Acetylcholine is a powerful excitotoxic neurotransmitter in the brain. By stimulating calcium-mobilizing receptors, acetylcholine, through G-proteins, stimulates phospholipase C and cause the hydrolysis of a membrane phospholipid...." "Inositol-1,4,5-triphosphate is important in cholinergic neuronal stimulation, and injury. Cholinergic agonists cause tonic-clonic convulsions which may be either transient or persistent. Even short-term cholinergic convusions may be associated with neuronal injury, especially in the basal forebrain and the hippocampus. Cholinergic-induced convulsions also elevate levels of brain calcium which precede neuronal injury. Female sex and senescence increase the sensitivity of rats to cholinergic excitotoxicity." "Furthermore, glutamate increases neuronal oxidative stress...."

L. N. Simanovskiy and Zh. A. Chotoyev, "The effect of hypoxia on glycogenolysis and glycolysis rates in the rat brain," Zhurnal Evolyutsionnoy Biokhimii i Fiziologii 6(5), 577-579, 1970. "Glycogenolysis and glycolysis in the whole brain of young and old rats were studied at sea level and under hypoxic conditions in a low-pressure chamber or at an altitude of 3,200 meters. The rate of carbohydrate metabolism increaased during postnatal development. In the absence of hypoxia, the rate of accumulation of lactate from either glycogen or glucose increases with maturation of the animals. The brain of young rats consumes primarily glycogen, particularly under anaerobic conditions." "Adaptation of mature rats to intermittent hypoxia is related to an increase in glycolysis, whereas adaptation of rats to high altitudes results in an increase in glycogenolysis. The type of carbohydrate metabolism is thus similar to the metabolism characteristic of the early stages of ontogenesis."

Ye. Sadovskiy, "For the prolongation of human life," Sovetskaya Belorussiya 23, page 4, Dec. 1970. "...the accumulation of metals in the organism with age is one of the most important factors in the development of the aging process."

Cerebral ischemia (and several other imbalances, relating to steroid regulation, shock) might be relieved by naloxone: D. S. Baskin and Y. Hosobuchi, Lancet ii, 272-275, 1981.

V. Reynolds, et al., "Heart rate variation, age, and behavior in subjects with senile dementia of Alzheimer type," Chronobiol. Int. 12(1), 37-45, 1995. "...circadian rhythm of SDAT may be more often unimodal than that of normal subjects of similar age, and that phase shift of the endogenous, clock-mediated component of the rhythm (with higher heart rate at night) is to be expected in a proportion of individuals with SDAT."

M. Martinez, et al., "Glucose deprivation increases aspartic acid release from synaptosomes of aged mice," Brain Res. 673(1), 149-152, 1995. "...in the absence of glucose in the medium of incubation aspartate and glutamate release was higher in old than in young animals." "...there is an age-dependent dysfunction in this process linked to energy metabolism disturbance."

J. M. Pasquini and A. M. Adamo, "Thyroid hormones and the central nervous system," Dev. Neurosci. 12(1-2), 1-8, 1994. "Among their actions, T3 and T4 have effects on the differentiation of various cell types in the rat brain and cerebellum as well as on the process of myelination. Recently, several investigators have shown effects of thyroid hormones on myelin protein gene expression."

G. C. Ness and Z. H. Zhao, "Thyroid hormone rapidly induces hepatic LDL receptor mRNA levels in hypophysectomized rats," Arch. Biochem. Biophys. 315(1), 199-202, 1994.

E. M. Mutisya, et al., "Cortical cytochrome oxidase activity is reduced in Alzheimer's disease," J. Neurochem. 63(6), 2170-2184, 1994. "These results provide further evidence of a cytochrome oxidase defect in Alzheimer's disease postmortem brain tissue. A deficiency in this key energy-metabolizing enzyme could lead to a reduction in energy stores and thereby contribute to the neurodegenerative process."

G. J. Bu, et al., "Subcellular localization and endocytic function of low density lipoprotein receptor-related protein in human glioblastoma cells," J. Biol. Chem. 269(47), 29874-29882, 1994. "Our results thus strongly suggest several potential roles for LRP in brain protein and lipoprotein metabolism, as well as control of extracellular protease activity."

V. Vandenbrouck, et al., "The modulation of apolipoprotein E gene expression by 3,3'-5-triiodothyronine in HepG(2) cells occurs at transcriptional and post-transcriptional levels," Eur. J. Biochem. 224(2), 463-471, 1994. "...thyroid hormone stimulated apoE gene transcription threefold in 24 hours."

T. Yamada, et al., "Apolipoprotein E mRNA in the brains of patients with Alzheimer's disease," J. Neurol. Sci. 129(1), 56-61, 1995. In A.D. Apo E "was decreased in relation to the apoE-epsilon 4 gene dosage." "AD patients who had long survival times showed high expression of apoE and low expression of GFAP [glial fibrillary acidic protein]. These results suggest that apoE suppresses the progression of AD, including gliosis, in the brain."

G. P. Jarvik, et al., "Genetic influences on age-related change in total cholesterol, low density lipoprotein-cholesterol, and triglyceride levels: Longitudinal apolipoprotein E genotype effects," Genet. Epidemiol. 11(4), 375-384, 1994. "Apo E is a component of LDL, is a ligand for the LDL receptor, and apo E genotype has been consistently associated with variation in mean levels of total cholesterol and LDL-C...." With aging, total cholesterol and LDL-C became significantly lower in the "epsilon 4 genotype" group; this is the group at risk for AD.

S. Miller and J. M. Wehner, "Cholesterol treatment facilitates spatial learning performance in DBA/2Ibg mice," Pharmacology Biochemistry and Behavior 49(1) 257-261, 1994. "Our results suggest that subchronic treatment with the steroid hormone precursor, cholesterol, enhances spatial learning performance in DBA mice."

A . D. Roses, "Apolipoprotein E affects the rate of Alzheimer disease expression: beta-amyloid burden is a secondary consequence dependent on ApoE genotype and duration of disease," J. Neuropathol. Exp. Neurol. 53(5), 429-437, 1994.

T. Gunther and V. Hollriegl, "Increased protein oxidation by magnesium deficiency and vitamin E depletion," Magnesium-Bull. 16(3), 101-103, 1994.

F. Oyama, et al., "Apolipoprotein E genotype, Alzheimer's pathologies and related gene expression in the aged population," Mol. Brain Res. 29(1), 92-98, 1995. "...ApoE4/4 accelerates and ApoE2/3 decelerates the development of the AD pathologies in the aged brain...."

M. L. C. Maatschieman, et al., "Microglia in diffuse plaques in hereditary cerebral hemorrhage with amyloidosis (Dutch). An immunohistochemical study," J. Neuropathol. Exp. Neurol. 53(5), 483-491, 1994. "Microglia are intimately associated with congophilic plaques in Alzheimer's disease...." "Intensely immunoreactive microglia with enlarged cell bodies and short, thick processes clustered in congophilic plaques."

J. Poirier, "Apolipoprotein E in animal models of CNS injury and in Alzheimer's disease," Trends Neurosci. 17(12), 525-530, 1994. "The coordinated expression of ApoE and its receptor...[low density lipoprotein (LDL)] receptor, appears to regulate the transport of cholesterol and phospholipids during the early and intermediate phases of the reinnervation process." "...a dysfunction of the lipid-transport system associated with compensatory sprouting and synaptic remodeling could be central to the AD process."

P. H. Chan and R. A. Fishman, "Brain edema: Induction in cortical slices by polyunsaturated fatty acids," Science 201, 358-369, 1978. "This cellular edema was specific, since neither saturated fatty acids nor a fatty acid containing a single double bond had such effect." R. Nogues, et al., "Influence of nutrition, thyroid hormones, and rectal temperature on in-hospital mortality of elderly patients with acut illness," Am J Clin Nutr 61(3), 597-602, 1995. "Serum albumin, body weight, and total T3 concentration were higher in survivors than in nonsurvivors." "Mild hypothermia was a good predictor of death. Hypoalbuminemia and hypothermia were associated with low T3 and high rT3 values."

R. C. Vannucci, et al., "Carbon dioxide protects the perinatal brain from hypoxic-ischemic damage: An experimental study in the immature rat," Pediatrics 95(6), 868-874, 1995.

H. M. Wisniewski and P. B. Kozlowski, "Evidence for blood-brain barrier changes in senile dementia of the Alzheimer type (SDAT)", Ann. N. Y. Acad. Sci. 396, 119-129, 1982. "...one would expect that the chronic "flooding" of the neuronal elements with serum proteins would affect their performance." "The cause of the increased BBB permeability in SDAT is unknown."

J. S. Jensen, et al., "Microalbuminuria reflects a generalized transvascular albumin leakiness in clinically healthy subjects," Clin. Sci. 88(6), 629-633, 1995. "It is suggested that the observed transvascular leakiness, in addition,may cause increased lipid insudation to the arterial walls."

C . Nilsson, et al., "The nocturnal increase in human cerebrospinal fluid production is inhibited by a beta(1)-receptor antagonist," Amer. J. Physiol.-Regul. Integr. C 36(6), R1445-R1448, 1994.

D. L. Williams, et al., "Cell surface 'blanket' of apolipoprotein E on rat adrenocortical cells," J. Lipid Res. 36(4), 745-758, 1995. "...the zona fasciculata cell is encircled or covered with apoE on all faces of the cell. ...this cell surface 'blanket' of apoE participates in the uptake of lipoprotein cholesterol by either the endocytic or selective uptake pathways." C. A. Frye and J. D. Sturgis, "Neurosteroids affect spatial reference, working, and long-term memory of female rats," Neurobiol. Learn. Memory 64(1), 83-96, 1995. [Female rats take longer to acquire a spatial task during behavioral estrus.)]

M. Warner and J. A. Gustafsson, "Cytochrome P450 in the brain: Neuroendocrine functions," Front Neuroendocrinol 16(3), 224-236, 1995. [Discusses the GABA(A) receptor active steroids, and the accumulation of pregnenolone in the brain.]

P. Robel, et al., "Biosynthesis and assay of neurosteroids in rats and mice: Functional correlates," J. Steroid Biochem. Mol. Biol. 53(1-6), 355-360, 1995. [Discusses the effects of pregnenolone and progesterone on aggression and learning. The animals which learned most easily had the highest levels of pregnenolone sulfate.] K. W. Lange and P. Riederer, "Glutamatergic drugs in Parkinson's disease," Life Sci. 55(25-26, 2067-2075, 1994. "...excitatory amino acids such as glutamate are involved in the pathophysiological cascade of MPTP...-induced neuronal cell death." "The 1-amino-adamantanes amantadine and memantine have recently been shown to be non-competitive NMDA antagonists and are widely used in Europe as antiparkinsonian agents."

R. A. Wallis, et al., "Glycine-induced CA1 excitotoxicity in the rat hippocampal slice," Brain Res. 664(1-2) 115-125, 1994. K. Ossawska, "The role of excitatory amino acids in experimental models of Parkinson's disease," J. Neural Transm.-Parkinsons 8(1-2_, 39-71, 1994.

G. S. Roth, et al., "Membrane alterations as causes of impaired signal transduction in Alzheimer's disease and aging," Trends Neurosci. 18, 203-206, 1995. "Reconstituted lipid membranes from cortical gray matter of AD brain samples were significantly thinner (that is, had less microviscosity) than corresponding age-matched controls." "This change in membrane width correlated with a 30% decrease in the moles of cholesterol:phospholipid." "Addition of cholesterol restored the membrane width to that of the age-matched control samples."

T. Reed, et al., "Lower cognitive performance in normal older adult male twins carrying the apolipoprotein E epsilon 4 allele," Arch. Neurol. 51(12), 1189-1182, 1994.

S.Y. Tan and M. B. Pepys, "Amyloidosis," Histopathology 25(5), 403-414, 1994. "...abnormal protein fibrils which are derived from different proteins in different forms of the disease. Asymptomatic amyloid deposition in a variety of tissues is a

universal accompaniment of ageing, and clinical amyloidosis is not rare. Intracerebral and cerebrovascular beta-protein amyloid deposits are a hallmark of the pathology of ... Alzheimer's disease...." "Amyloid deposits are in a state of dynamic turnover and can regress if new fibril formation is halted." A. V. Sirotkin, "Direct influence of melatonin on steroid, nonapeptide hormones, and cyclic nucleotide secretion by granulosa cells isolated from porcine ovaries," J. Pineal Res. 17(3), 112-117, 1994. "It was found that melatonin is able to inhibit progesterone and stimulate estradiol secretion." "Some inhibition of vasopressin and cAMP and significant stimulation of cGMP also resulted from melatonin treatment." R. M. Sapolsky, "Glucocorticoid toxicity in the hippocampus: Reversal with supplementation with brain fuels," J. Neurosci. 6, 2240-2245, 1986. R. M. Sapolsky, "Glucocorticoids, hippocampal damage and the glutaminergic synapse," Prog. Brain Res. 86, 13-23, 1990. M. Schwartz, et al., "Growth-associated triggering factors and central nervous system regeneration," p. 47 in Trophic Factors and the Nervous System, edited by L. A. Horrocks, et al., Raven Press, NY, 1990. R. W. Ordway, et al., "Direct regulation of ion channels by fatty acids," Trends Neurosci. 14, 96-100, 1991.

H. G. P. Swarts, et al., "Binding of unsaturated fatty acids to Na+,K+-ATPase leading to inhibition and inactivation," Biochim. Biophys. Acta 1024, 32-40, 1990.

G. Autore, et al., "Essential fatty acid-deficient diet modifies PAF levels in stomach and duodenum of endotoxin-treated rats," J. Lipid Mediators Cell Signalling 9, 145-153, 1994. J. Rafael, et al., "The effect of essential fatty acid deficiency on basal respiration and function of liver mitochondria in rats," J. Nutr. 114, 255-262, 1984.

A. M. Weiner, et al., "Nonviral retroposons, genes, pseudogenes, and transposable elements generated by the reverse flow of genetic information," Ann. Rev. Biochem. 55, 631-661, 1986. I. Zs.-Nagy, "Semiconduction of proteins as an attribute of the living state: The ideas of Albert Szent-Gyorgyi revisited in light of the recent knowledge regarding oxygen free radicals," Exp. Gerontology 30(3-4), 327-335, 1995. "In this assumption, the continuous radical flux is as important for the maintenance of the living state, as the voltage power supply is essential for the functioning of the computer."

Winfried G. Rossmanith, "Gonadotropin secretion during aging in women: Review article," Exp. Gerontology 30(3/4) 369-381, 1995. "...major functional derangements, primarily at a hypothalamic rather than a pituitary site, have been determined as concomitants of aging in women." "...aging may impair the negative feedback sensitivity to ovarian sex steroids...." Hormonal changes at menopause "may represent the sum of functional aberrations that were initiated much earlier in life...." "...prolonged estrogen exposure facilitates the loss of hypothalamic neurons...."

J. R. Brawer, et al., "Ovary-dependent degeneration in the hypothalamic arcuate nucleus," Endocrinology 107, 274-279, 1980.

G. C. Desjardins, "Estrogen-induced hypothalamic beta-endorphin neuron loss: A possible model of hypothalamic aging," Exp. Gerontology 30(3/4), 253-267, 1995. "This loss of opioid neurons is prevented by treatment with antioxidants indicating that it results from estradiol-induced formation of free radicals." "...this beta-endorphin cell loss is followed by a compensatory upregulation of mu opioid receptors in the vicinity of LHRH cell bodies." Resulting supersensitivity of the cells results "in chronic opioid suppression of the pattern of LHRH release, and subsequently that of LH." The neurotoxic effects of estradiol cause a "cascade of neuroendocrine aberrations resulting in anovulatory acyclicity." Treatment with an opiod antagonist "reversed the cystic morphology of ovaries and restored normal ovarian cycles" in estrogen-treated rats.

G. B. Melis, et al., "Evidence that estrogens inhibit LH secretion through opioids in postmenopausal women using naloxone," Neuroendocrinology 39, 60-63, 1984.

H. J. Sipe, et al., "The metabolism of 17 beta-estradiol by lactoperoxidase: A possible source of oxidative stress in breast cancer," Carcinogenesis 15(11), 2637-2643, 1994. "...molecular oxygen is consumed by a sequence of reactions initiated by the glutathione thiyl radical. ...the estradiol phenoxyl radical abstracts hydrogen from...NADH to generate the NAD radical." "...the futile metabolism of micromolar quantities of estradiol catalyzes the oxidation of much greater concentrations of biochemical reducing cofactors, such as glutathione and NADH, with hydrogen peroxide produced as a consequence."

S. Santagati, et al., "Estrogen receptor is expressed in different types of glial cells in culture," J. Neurochem. 63(6), 2058-2064, 1994. "...in all three types of glial cell analyzed in almost equal amounts..."

D. X. Liu and L. P. Li, "Prostaglandin F-2 alpha rises in response to hydroxyl radical generated in vivo," Free Radical Biol. Med. 18(3), 571-576, 1995. "Free radicals and some free fatty acids, such as arachidonic acid metabolites...may form a feedback loop in which generation of one type leads to formation of the other." "Prostaglandin F-2 alpha dramatically increased in response to hydroxyl radical generation...."

J. Owens and P. A. Schwartzkroin, "Suppression of evoked IPSPs by arachidonic acid and prostaglandin F-2 alpha," Brain Res. 691(1-2), 223-228, 1995. "These findings suggest that high levels of AA and its metabolites may bias neurons towards excitation."

E. A. Quail and G. C. T. Yeoh, "The effect of iron status on glyceraldehyde 3-phosphate dehydrogenase expression in rat liver," FEBS Lett. 359(2-3), 126-128, 1995. "...the overexpression of GAPDH mRNA in iron deficiency is probably due to increased message stability." [This is one of the points discussed by Henics. Estrogen, which increases iron retention, also modifies mRNA stability.]

J. G. Liehr, et al., "4-hydroxylation of estradiol by human uterine myometrium and myoma microsomes: Implications for the mechanism of uterine tumorigenesis," Proc Natl Acad Sci USA 92(20), 9220-9224, 1995. "... elicits biological activities distinct from estradiol, most notably an oxidant stress response induced by free radicals generated by metabolic redox cycling reactions."

J. G. Liehr and D. Roy, "Free radical generation by redox cycling of estrogens," Free Rad. Biol. Med. 8, 415-423, 1990.

P. Aschheim, "Resultats fournis par la greffe heterochrone des ovaires dan l'etude de la regulation hypothalamo-hypophyso-ovarienne de la ratte senile," Gerontologia 10, 65-75, 1964/65. "Our last experiment, grafting ovaries...into senile rats which had been castrated (ovariectomized) when young, and its result, the appearance of estrous cycles, seems explicable by this hypothesis. Everything happens as if the long absence of ovarian hormones... had kept the cells of the hypothalamus in the state of youth. It's as if the messages of the circulating steroids fatigued the hypothalamic memory." "What are the factors that cause this diminution of the hypothalamic sensitivity...? Kennedy incriminates a decrease in the cellular metabolism in general...."

P. Ascheim, "Aging in the hypothalamic-hypophyseal ovarian axis in the rat," pp. 376-418 in: A. V. Everitt and J. A. Burgess, editors, Hypothalamus, Pituitary and Aging, C>C> Thomas, Springfield, 1976.

Gross, "Reproductive cycle biochemistry," Fertility & Sterility 12(3), 245-260, 1961. "The maintenance of an environment conducive to anaerobic metabolism--which may involve the maintenance of an adequate supply of the substances that permit anaerobiosis...seems to depend primarily upon the action of estrogen." "Glycolytic metabolism gradually increases throughout the proliferative phases of the cycle, reaching a maximum coincident with the ovulation phase, when estrogen is at a peak. Following this, glycolysis decreases, the respiratory mechanisms being more active during the secretory phase. Eschbach and Negelein showed the metabolism of the infantile mouse uterus to be less anaerobic than that of the adult. If estrogen is administered, however, there is a 98 per cent increase in glycolytic mechanisms.""The effect of the progestational steroids may be such as to interfere with the biochemical pattern required for support of this anaerobic environment."

C. S. Bangur, J. L. Howland, S. S. Katyare, "Thyroid hormone treatment alters phospholipid composition and membrane fluidity of rat brain mitochondria," Biochem. J. 305(1), 29-32, 1995. (Increases fluidity.)

R. S. Sohal, et al., "Mitochondrial superoxide and hydrogen peroxide generation, protein oxidative damage, and longevity in different species of flies," Free Rad. Biol. & Med. 19(4), 499-504, 1995. Cytochrome C oxidase protects against free radical damage. This enzyme depends on thyroid and light.

D. L. Williams, et al., "Cell surface 'blanket' of apolipoprotein E on rat adrenocortical cells," J. Lipid Res. 36(4), 745-758, 1995. "...the zona fasciculata cell is encircled or covered with apoE on all faces of the cell. ...this cell surface 'blanket' of apoE participates in the uptake of lipoprotein cholesterol by either the endocytic or selective uptake pathways."

C. A. Frye and J. D. Sturgis, "Neurosteroids affect spatial reference, working, and long-term memory of female rats," Neurobiol. Learn. Memory 64(1), 83-96, 1995. [Female rats take longer to acquire a spatial task during behavioral estrus.] M. Warner and J. A. Gustafsson, "Cytochrome P450 in the brain: Neuroendocrine functions," Front Neuroendocrinol 16(3), 224-236, 1995. [Discusses the GABA(A) receptor active steroids, and the accumulation of pregnenolone in the brain.]

P. Robel, et al., "Biosynthesis and assay of neurosteroids in rats and mice: Functional correlates," J. Steroid Biochem. Mol. Biol. 53(1-6), 355-360, 1995. [Discusses the effects of pregnenolone and progesterone on aggression and learning. The animals which learned most easily had the highest levels of pregnenolone sulfate.]

J. R. Pasqualini, et al., "Effect of the progestagen promegestone (R-5020) on mRNA of the oestrone sulphatase in the MCF-7 human mammary cancer cells," Anticancer Res. 14(4A), 1589-1593, 1994. Progestagen decreases estrogen sulfatase in mammary cancers. [Sulfatase, like beta-glucuronidase, causes active estrogen to be released.]

W. J. Trooster, et al., "Treatment of acute experimental allergic encephalomyelitis in the Lewis rat with the sex hormone progesterone," Int. J. Immunopathol. Pharmacol. 7(3), 183-192, 1994. "...we suggest that treatment with progesterone protected against the histological signs of EAE through a peripheral immune mechanism."

H. L. Koenig, et al., "Progesterone synthesis and myelin formation by Schwann cells," Science (268), 1500-1503, 1995. "The high concentrations of progesterone in intact adult nerves also indicate a role for this neurosteroid in the slow but continuous renewal of peripheral myelin."

N. C. Lan and K. W. Gee, "Neuroactive steroid actions at the GABA(A) receptor," Horm. Behav. 28(4), 537-544, 1994. Neuroactive steroids "...do not interact with any of the classical cytosolic hormonal steroid receptors." "The interaction of neuroactive steroids with GABA(A) receptor is specific to a site on the receptor complex distinct from the benzodiazepine and barbiturate modulatory sites."

J. F. FierroRenoy, et al., "Three different thyroid hormone receptor isoforms are detected in a pure culture of ovine oligodendrocytes," Glia 14(4), 322-328, 1995. "Our results demonstrate that differentiated oligodendrocytes express alpha-1 and alpha-2 variant and beta-1 isoforms of TH at the protein level and support the notion of a direct impact of thyroid hormones on oligodendrocytes in their regulation of myelin synthesis."

J. Masse, "Nutrition, thyroid hormones, body temperature, and mortality of elderly patients with acute illnesses," Am. J. Clin. Nutr. 62(3), 647-648, 1995.

E. J. Masoro, "Dietary restriction," Exp. Gerontology 30(3/4), 291-298, 1995. "These antiaging actions result from a reduction of energy intake by the animal but are not due to a decrease in metabolic rate per unit of lean body mass." [The slowed rate of aging is associated with increased metabolic rate--as if metabolic inhibitors accumulate at a slower rate.]

D. L. Cheney, et al., "Pregnenolone sulfate antagonizes dizocilpine amnesia: Role for allopregnanolone," Neuroreport 6(12), 1697-1700, 1995. "We and others have shown that allopregnanolone potently modulate GABA(A) receptor function whereas 5 alpha-dihydroprogesterone fails to induce rapid changes...."

B. S. McEwen and E. Gould, "Adrenal steroid influences on the survival of hippocampal neurons," Biochem. Pharmacol 40,

2393-2402, 1990.

P. W. Landfield, et al., "Hippocampal aging and adrenocorticoids: Quantitative correlations," Science 202(8), 1098-1101, 1978.

A. M. Dudchenko, et al., "Effect of corticosterone on the macroergic pool and membrane permeability in sections of rat hippocampus," Bull. Exp. Biol. & Med. 116(12), 1505-1508, 1993. "...the hippocampus is one of the most vulnerable brain structures...." "...a reduction of the oxygen content...causes a sharp increase of membrane permeability, which is...in line with the trend toward a decrease of the macroergic [energy] content (especially creatine phosphate and ATP content) in the hippocampal cells." "The death of hippocampal neurons, triggered...by hyperactivation of the glutamate receptors, is accelerated in the presence of" glucocorticoids, while these hormones may be protective against oxygen deficit, by increasing the availability of glucose, and possibly of amino acids.

M. J. Meaney, et al., "Individual differences in hypothalamic-pituitary-adrenal activity in later life and hippocampal aging," Exp. Gerontology 30(3/4), 229-251, 1995. "...glucocorticoids...both increase the toxic glutamate signal and decrease the metabolic capacity of neurons to survive." (Glucose is protective.) "Our current foxus is on the potential role of progesterone as a modulator of glucocorticoid action."

P. Sheng, et al., "Methamphetamine causes reactive gliosis in vitro: Attenuation by the ADP-ribosylation inhibitor, benzamide," Life Sciences 55(3), 51-54, 1994

N. S. Verkhratsky, "Limbic control of endocrine glands in aged rats," Exp. Gerontology 30(3/4, 415-421, 1995. Aging causes "degeneration of pyramidal cells in the hippocampus of humans..., accumulation of lipofuscin...,a decrease in the excitability of amygdala medial nuclei and an increased excitability of its central nuclei..., and a deterioration of their vascularization." "...stimulation of hippocampus inhibits ACTH secretion...and causes a decrease of plasma corticosteroids...."

R. M. Sapolsky, et al., "Prolonged glucocorticoid exposure reduces hippocampal neuron number: Implications for aging," J. Neurosci. 5 1221, 1985.

J. L. W. Yau, Mol. Brain Res. 27(1), 174-178, 1994. "Glucocorticoid excess is associated with hippocampal neuronal dysfunction and loss, mainly affecting CA1."

B. Nasman, et al., "A subtle disturbance in the feedback regulation of the hypothalamic-pituitary-adrenal axis in the early phase of Alzheimer's disease," Psychoneuroendocrinology 20(20, 211-220, 1995. "After 0.5 mg dexamethasone, serum cortisol levels were significantly less suppressed...."

C. Mondadori, "In search of the mechanism of action of the nootropics: New insights and potential clinical implications," Life Sci. 55(25-26), 2171-2178, 1994. "...the fact that high levels of corticosteroids suppress the effects of the nootropics could also have clinical implications: in the light of the observation that the majority of Alzheimer patients have elevated steroid levels it could explain why there is always only a small proportion of patients...that respond to treatment with nootropics."

J. M. Pasquini and A. M. Adamo, "Thyroid hormones and the central nervous system," Dev. Neurosci. 12(1-2), 1-8, 1994. "Among their actions, T3 and T4 have effects on the differentiation of various cell types in the rat brain and cerebellum as well as on the process of myelination. Recently, several investigators have shown effects of thyroid hormones on myelin protein gene expression."

M. Martinez, et al., "Glucose deprivation increases aspartic acid release from synaptosomes of aged mice," Brain Res. 673(1), 149-152, 1995. "...in the absence of glucose in the medium of incubation aspartate and glutamate release was higher in old than in young animals." "...there is an age-dependent dysfunction in this process linked to energy metabolism disturbance."

P. Corbisier, et al., "Bioenergetics of mitochondria determine cell survival in stressful conditions," Prog. in Cell Res. (5), 237-241, 1995. "...the growth rate of young or old cells injected with coupled mitochondria...was not statistically different."

G. Paradies, et al., "Molecular basis of the age-dependent decrease in the cytochrome oxidase activity in rat heart mitochondria," Prog. in Cell Res. 5, 243-247, 1995. The activity of cytochrome oxidase "was markedly decreased with aging. This decrease was associated with a parallel decrease in the mitochondrial respiratory activity." "Cardiolipin content was significantly reduced in mitochondrial membrane from aged rats."

G. C. Ness and Z. H. Zhao, "Thyroid hormone rapidly induces hepatic LDL receptor mRNA levels in hypophysectomized rats," Arch. Biochem. Biophys. 315(1), 199-202, 1994.

E. M. Mutisya, et al., "Cortical cytochrome oxidase activity is reduced in Alzheimer's disease," J. Neurochem. 63(6), 2170-2184, 1994. "These results provide further evidence of a cytochrome oxidase defect in Alzheimer's disease postmortem brain tissue. A deficiency in this key energy-metabolizing enzyme could lead to a reduction in energy stores and thereby contribute to the neurodegenerative process."

G. J. Bu, et al., "Subcellular localization and endocytic function of low density lipoprotein receptor-related protein in human glioblastoma cells," J. Biol. Chem. 269(47), 29874-29882, 1994. "Our results thus strongly suggest several potential roles for LRP in brain protein and lipoprotein metabolism, as well as control of extracellular protease activity."

V. Vandenbrouck, et al., "The modulation of apolipoprotein E gene expression by 3,3'-5-triiodothyronine in HepG(2) cells occurs at transcriptional and post-transcriptional levels," Eur. J. Biochem. 224(2), 463-471, 1994. "...thyroid hormone stimulated apoE gene transcription threefold in 24 hours."

M. J. Ignatius, et al. "Expression of apolipoprotein-E during nerve degeneration and regeneration," Proc. Natl. Acad. Sci. (USA) 83, 1125-1129, 1986.

B. T. Stokes, et al., "Energy depletion, calcium and the cytoskeleton: A model for trophic intervention," pp. 279-292, in Trophic Factors and the Nervous System, L. A. Horrocks, et al., editors, Raven Press, NY, 1990. "Injury to neuronal cells is associated with a decline in high energy phosphates, a loss of cation homeostasis, and possibly, an increase in reactive oxygen radicals." "Virtually all components of the cytoskeleton are either directly or indirectly affected by alterations in calcium metabolism." "...calcium-activated proteases may also specifically modulate components of the cytoskeleton." "...ATP depletion itself may directly alter the structural components of the neuronal cytoskeleton." "...major neurodegenerative diseases such as Alzheimer's, Parkinsonian syndrome, amyotrophic lateral sclerosis...are also characterized by changes in the neuronal cytoskeleton."

T. Gunther, et al., "Effects of magnesium and iron on lipid peroxidation in cultured hepatocytes," Mol. Cell Biochem. 144(2), 141-145, 1995. (Magnesium protects against iron.)

K. D. Croft, et al., "Oxidation of low-density lipoproteins: Effect of antioxidant content, fatty acid composition and intrinsic phospholipase activity on susceptibility to metal ion-induced oxidation," BBA-Lipid Lipid Metab. 1254(3), 250-256, 1995.

J. H. Choi and B. P. Yu, "Brain synaptosomal aging: Free radicals and membrane fluidity," Free Radical Biol. Med. 18(2), 133-139, 1995 ("...fluidity loss may be influenced by factors other than cholesterol. We suggest that lipid peroxidation may be a major factor in the change in fluidity during the aging process.")

J. H. Choi and B. P. Yu, "Modification of age-related alterations of iron, ferritin, and lipid peroxidation in rat serum," Age 17(3), 93-97, 1994.

E. Chiarpotto, et al., "Metabolism of 4-hydroxy-2-nonenal and aging," Biochem. Biophys. Res. Commun. 297(2), 477-484, 1995. (Accumulation of unsaturated fat breakdown product in old animals.)

H. J. Sipe, et al., "The metabolism of beta-estradiol by lactoperoxidase: A possible source of oxidative stress in breast cancer," Carcinogenesis 15(11), 2637-2643, 1994.

M. J. Endresen, et al., "Effects of free fatty acids found increased in women who develop pre-eclampsia on the ability of endothelial cells to produce prostacyclin, cGMP and inhibit platelet aggregation," Scan. J. Clin. Lab. Invest. 54(7), 549-557, 1994. "...levels of circulating free fatty acids are increased in women who later develop pre-eclampsia long before the clinical onset of the disease." "...linoleic acid reduced the thrombin-stimulated prostacyclin release by 30-60%, oleic acid by 10-30%, wheras palmitic acid had no effect." "Linoleic acid reduced the endothelial cells" ability to inhibit platelet aggregation by 10-45%...."

L. A. Norris and J. Bonnar, "Effect of oestrogen dose on whole blood platelet activation in women taking new low dose oral contraceptives," Thromb. Haemost. 72(6), 926-930, 1994: "Increased levels of ADP and arachidonic acid-induced aggregation were observed in women taking the 30 microgram ethinyloestradiol combination. Platelet release of beta-thromboglobulin (beta TG) was also significantly increased. Increased collagen-induced aggregation was observed but this failed to reach statistical significance for the individual treatment groups.") Estrogen dominance is an essential factor in preeclampsia. Women who have died of (eclamptic) convulsions have been found to have massive clots in their brain blood vessels. Much of this work had its origin in the 1930s (Shute and others), and was buried by the power of the estrogen industry.

H. Darmani, et al., "Interferon-gamma and polyunsaturated fatty acids increase the binding of lipopolysaccharide to macrophages," Int. J. Exp. Pathol. 75(5), 363-368, 1994.

G. Autore, et al., "Essential fatty acid-deficient diet modifies PAF levels in stomach and duodenum of endotoxin-treated rats," J. Lipid Mediators Cell Signalling 9, 145-153, 1994. Deficiency of "essential" fats decreases damage from endotoxin.

N. Auge, et al., "Proliferative and cytotoxic effects of mildly oxidized low-density lipoproteins on vascular smooth-muscle cells," Biochem. J. 309(Part 3), 1015-1020, 1995. "The proliferative effect on smooth-muscle cells is counterbalanced at high concentrations of mildly oxidized LDLs (or at high oxidation levels) by their cytotoxic effect."

S. K. Clinton, et al., "The combined effects of dietary fat and estrogen on survival, 7,12-dimethyl- benz(a)-anthracene-induced breast cancer and prolactin metabolism in rats," J. Nutr. 125(5), 1192-1204, 1995. "Mortality in controls was doubled by feeding a high fat diet...." "...the presence of estrogen may be a prerequisite for significant dietary modulation."

R. Sanchez Olea, et al., "Inhibition by polyunsaturated fatty acids of cell volume regulation and osmolyte fluxes in astrocytes," Amer. J. of Physiology--cell physiology 38(1), C96-C102, 1995. "...potent blockers of regulatory volume decrease and of the swelling-activated efflux of taurine, D-aspartate, inositol, and I-125 (used as marker of Cl). ...oleic and ricinoleic acids and saturated fatty acids were ineffective." "...polyunsaturated fatty acids directly inhibit the permeability pathways correcting cell volume after swelling in cultured astrocytes."

M. E. Miller, et al., "Influence of hormones on platelet intracellular calcium," Thrombosis Research 77(6), 515-530, 1995. "Platelet intracellular calcium concentration and release was significantly decreased in women ingesting tamoxifen compared to controls and significantly increased, as was platelet adhesion, in oral contraceptive users." "Only oral contraceptive users had increased sensitivity to aggregating agents. (...platelet calcium levels are closely related to the degree of platelet adhesion and aggregation in vivo."

F. Mercure and G. Vanderkraak, "Inhibition of gonadotropin-stimulated ovarian steroid production by PUFA in teleost fish,"

Lipids 30(6), 547-554, 1995. "EPA and DHA inhibited gonadotropin-stimulated testosterone production in a dose-related manner...."

A A Farooqui, K Wells, L A Horrocks, "Breakdown of membrane phospholipids in Alzheimer disease--involvement of excitatory amino acid receptors," Mol Chem Neuropathol 25(2-3) 155-173, 1995. "The release of arachidonate from the sn-2 position of glycerophospholipids is catalyzed by phospholipases and lipases. These enzymes are coupled to EAA receptors. Overstimulation of these receptors may be involved in abnormal calcium homeostasis, degradation of membrane phospholipids, and the accumulation of free fatty acids, prostaglandins, and lipid peroxides. Accumulation of the mentioned metabolites, as well as abnormalities in signal transduction owing to stimulation of lipases and phospholipases, may be involved in the pathogenesis of the neurodegeneration in AD."

Leo Loeb, V. Suntzeff, and E. L. Burns, "Changes in the nature of the stroma in vagina, cervix and uterus of the mouse produced by long-continued injections of estrogen and by advancing age," The American Journal of Cancer 35(2), 159-174, 1939. Loeb, et al., speak of collagenous deposits as fibrous-hyaline tissue, varying from a fibrillar to a homogeneous appearance, and varying in consistency from very dense and glassy in appearance, to the softer gelatinous substance between cells and around arteries and glands. This material increases with aging and eventually appears between cells in the muscular part of the uterus. With the injection of moderate amounts of estrogen, the quantity of the material is increased. When large amounts of estrogen are injected, "The connective tissue and muscle appear rarefied, almost as though they were perforated by a large number of small holes." "...this condition is presumably due to a deposit of a mixture of hyaline material and edematous fluid...." "This process of hyalinization...is counteracted by invasion by connective tissue." In this way there may take place in many areas a substitution and organization of the hyaline material by connective tissue, in which dilated capillaries may also be visible." "There is a second process which in many cases accompanies the invasion and organization of hyaline substance by connective tissue, namely a formation, at the margin of the hyaline material, of epithelioid and of small giant cells possessing more than one nucleus." "As a rule, the epithelioid cells are seen alone; giant cells are more rare." "...the connective-tissue fibrils may in places appear somewhat separated, perhaps by edematous fluid." "The first changes consist very likely in the transudation of fluid from the vessels into the connective tissue." "It seems, then, that at a very early stage after the beginning of the injections of effective doses of estrogen, a liquid substance which separates the connective-tissue elements makes its appearance, and that this represents one of the earliest changes induced by the hormone. It may be accompanied, or soon followed, by the deposit of a hyaline substance which occurs first between the connective-tissue cells, but may extend also to the muscle fibers." "...the deposit of hyaline which progressively becomes more and more devoid of connective-tissue cells and blood vessels, is so marked that the material acts like a foreign body...." "While it may be found also around blood vessels, such deposits are less conspicuous than in other organs in mice, such as the mammary gland.... There is a tendency for the hyaline substance to form sheaths around various organs and it is more prominent at the border separating different tissues and organs." "In its appearance and in the foreign body reactions which it initiates this substance somewhat resembles amyloid, which is readily produced in mice in various groups. The application of stains differentiating amyloid from other hyaline material, however, gave negative results."

Leo Loeb, V. Suntzeff, and E. L. Burns, "The effects of age and estrogen on the stroma of vagina, cervix and uterus in the mouse," Science 88(22, Nov. 4), 1938. "...large amounts of a hyaline substance are deposited, which act as foreign bodies and cause the formation of epithelioid and giant cells and an ingrowth of connective tissue. Thus an organization of this substance is attempted, which is interrupted, however, by renewed deposition of this hyaline material." "No definite statement can be made at present as to the chemical nature of this substance and its possible relation to a plasma constituent, except that it is not amyloid." "...a very intense fibrosis and hyalinization of the stroma which may induce abnormal reactions in the surrounding tissue. In this way it seems to be possible to accelerate and intensify very much some of the old age changes in certain organs."

P. H. Chan and R. A. Fishman, "Brain edema: Induction in cortical slices by polyunsaturated fatty acids," Science 201, 358-369, 1978. "This cellular edema was specific, since neither saturated fatty acids nor a fatty acid containing a single double bond had such effect."

C. LarssonBackstrom, et al., "Effects of dietary alpha- and gamma-linolenic acids on liver fatty acids, lipid metabolism, and survival in sepsis," Shock 4(1), 11-20, 1995. "Dietary GLA reduced survival from sepsis."

D. Chemla, et al., "Influence of dietary polyunsaturated fatty acids on contractility, inotropy and compliance of isolated rat myocardium, J mol Cell Cardiol 27(8), 1745-1755, 1995. "There was a trend towards a lower peak lengthening velocity at preload in the LC (n-3) group...together with an unchanged peak rate of isometric force decline. This resulted in a significant impairment of the two mechanical indexes testing the load dependence of myocardial relaxation." See B. Pieske, Circul. 92(5), 1169-78

R. Lerner, et al., "Development and characterization of essential fatty acid deficiency in human endothelial cells in culture," Proc Natl Acad Sci USA 92(4), 1147-1151, 1995. Oleic acid derivative 5,8,11-eicosatrienoic acid (20:3 omega 9) (5,8,11,14,17 eicosapentaenoic, 20-5 omega 3)); 20:3 omega 9 impaired the Ca2(i) response, indicating a suppressive effect of it. (Agonist-induced increases in concentrations of prostacycline PGI 2, and cytosolic Ca2+ were reduced in efad cells.)

K. Imaizumi, et al., "Dissociation of protein kinase C activities and diacylglycerol levels in liver plasma membranes of rats on coconut oil and safflower oil diets," J. Nutr Biochem 6(10), 528-533, 1995. "The activation of PKC is affected differently in vitro by different fatty acids." "Rats on coconut oil...had a markedly lower PKC activity in liver plasma membranes with slight but significant reduction of the activity in the cytosol than did rats fed safflower oil...." "...coconut oil resulted in a higher content of diacylglycerols in these membranes than did ingestion of safflower oil, whereas the proportions of saturated fatty acids and phospholipids and membrane fluidity were similar between rats ingesting different fats." "It seems likely that saturated fats exert various physiological effects on lipid and lipoprotein metabolism, in part through PKC pathways."

V. Boutard, et al., "Fish oil supplementation and essential fatty acid deficiency reduce nitric oxide synthesis by rat

macrophages," Kidney Int. 46(5), 1280-1286, 1994. "Both...have been shown to exert anti-inflammatory effects...."

A A Farooqui, K Wells, L A Horrocks, "Breakdown of membrane phospholipids in Alzheimer disease--involvement of excitatory amino acid receptors," Mol Chem Neuropathol 25(2-3) 155-173, 1995. "The release of arachidonate from the sn-2 position of glycerophospholipids is catalyzed by phospholipases and lipases. These enzymes are coupled to EAA receptors. Overstimulation of these receptors may be involved in abnormal calcium homeostasis, degradation of membrane phospholipids, and the accumulation of free fatty acids, prostaglandins, and lipid peroxides. Accumulation of the mentioned metabolites, as well as abnormalities in signal transduction owing to stimulation of lipases and phospholipases, may be involved in the pathogenesis of the neurodegeneration in AD."

P. H. Chan and R. A. Fishman, "Transient formation of superoxide radicals in polyunsaturated fatty acid-induced brain swelling," J. of Neurochemistry 35, 1004-1007, 1980.

J. S. Jensen, et al., "Microalbuminuria reflects a generalized transvascular albumin leakiness in clinically healthy subjects," Clin Sci 88(6), 629-633, 1995. "In epidemiological studies microalbuminuria, i.e., slightly elevated urinary albumin excretion rate, predicts increased atherosclerotic vascular morbidity and mortality." "In animal experiments the outflux of albumin and lipids to the arterial wall are highly correlated, and both are elevated in atherosclerosis." "...microalbuminuria is an independent marker of systemic transvascular albumin leakiness in clinically healthy subjects."

H. M. Wisniewski and P. B. Kozlowski, "Evidence for blood-brain barrier changes in senile dementia of the alzheimer type (SDAT)", Ann. N. Y. Acad. Sci. 396, 119-129, 1982. "...one would expect that the chronic "flooding" of the neuronal elements with serum proteins would affect their performance." "The cause of the increased BBB permeability in SDAT is unknown."

F. Laszlo, et al., "Association of microvascular leakage with induction of nitric oxide synthase: Effects of nitric oxide synthase inhibitors in various organs," Eur. J. Pharmacol. 283(1-3), 47-53, 1995. "...assessed by the vascular leakage of ... albumin." "Endotoxin...induced the expression of a calcium-independent nitric oxide synthase...."

C. Nilsson, et al., "The nocturnal increase in human cerebrospinal fluid production is inhibited by a beta(1)-receptor antagonist," Amer. J. Physiol.--Regul. Integr. C 36(6), R1445-R1448, 1994.

S. Capsoni, et al., "Reduction of regional cerebral blood flow by melatonin in young rats," Neuroreport 6(9), 1346-1348, 1995. "...reduced in the cerebral areas supplied by circle of Willis and the basilar arteries. [Also to the] ...choroid plexuses."

A. C. Bowling and M. F. Beal, "Bioenergetic and oxidative stress in neurodegenerative diseases," Life Sci. 56(14), 1151-1171, 1995. "Defects in energy metabolism and increased cortical lactate levels have been detected in Huntington's disease patients. Studies of Alzheimer's disease patients have identified decreased [mitochondrial] complex IV activity...." "The age-related onset and progressive course of these neurodegenerative diseases may be due to a cycling process betwen impaired energy metabolism and oxidative stress."

K. Nakai, et al., "Regeneration of norepinephrine-containing fibers in occipital cortex of adult cats," Brain Res. Bull. 35(5-6), 409-412, 1994. "The present results indicate that the regenerative ability of the central NE neurons is universal, not limited to the immature brain. ...equipped with a transmitter-specific repair mechanism throughout life."

A. Bhatnagar, "Biochemical mechanism, of irreversible cell injury caused by free radical-initiated reactions," Mol. Cell. Biochem. 137(1), 9-16, 1994. "...free radical-induced irreversible cell injury results from a loss of protein thiols."

L. Balazs and M. Leon, "Evidence of an oxidative challenge in the Alzheimer's brain," Neurochem. Res. 19(9), 1131-1137, 1994. "These data suggest that the entire Alzheimer's brain may be subject to an oxidative challenge, but that some brain areas may be more vulnerable than others to the consequent neural damage that characterizes the disease."

J. A. Court and E. K. Perry, "CNS nicotinic receptors--possible therapeutic targets in neurodegenerative disorders," CNS Drugs 2(3), 216-233, 1994. "...epidemiological evidence suggests that later in life tobacco smoking may offer some protection against Parkinson's and Alzheimer's diseases."

N. A. Simonian and B. T. Hyman, "Functional alterations in Alzheimer's disease: Selective loss of mitochondrial-encoded cytochrome oxidase mRNA in the hippocampal formation," J. Neuropathol. Exp. Neurol. 53(5), 508-512, 1994.

A. M. Proenze, et al., "Estrogen effects on blood amino acid compartmentation," Life Sci. 57(17), 1589-1587, 1995.

S. S. Smith, "Sensorimotor-correlated discharge recorded from ensembles of cerebellar Purkinje cells varies across the estrous cycle of the rat," J. Neurophysiol. 74(3), 1095-1108, 1995. "...estradiol augments excitatory responses of cerebellar Purkinje cells to...glutamate...."

C. F. Lim, et al., "Influence of nonesterified fatty acid and lysolecithins on thyroxine binding to thyroxine-binding globulin and transthyretin," Thyroid 5(4), 319-324, 1995. "Unsaturated nonesterified fatty acids...inhibited T4 binding to TBG." "Saturated NEFAs...were inactive."

O. V. Sviridov, "Specific binding of thyroid hormones by human plasma apolipoproteins: A new property of known proteins," Biochemistry (Engl. translation) 59(5), 457-466, 1884.

T. Parasassi, et al., "Cholesterol protects the phospholipid bilayer from oxidative damage," Free Radical Biology & Medicine 19(4), 511-516, 1995.

A. G. Herzog, "Progesterone therapy in women with complex partial and secondary generalized seizures," Neurology 45(9),

1660-1662, 1995.

Z. Q. Ma, et al., Estrogenic control of monoamine oxidase A activity in human neuroblastoma cells expressing physiological concentrations of estrogen receptor," Eur. J. Pharmacol. 284(1-2), 171-176, 1995.

J. G. Belasco and G. Brawerman, Control of Messenger RNA Stability, Academic Press, NY, 1994.

Leo Loeb, V. Suntzeff, and E. L. Burns, "Changes in the nature of the stroma in vagina, cervix and uterus of the mouse produced by long-continued injections of estrogen and by advancing age," The American Journal of Cancer 35(2), 159-174, 1939. Loeb, et al., speak of collagenous deposits as fibrous-hyaline tissue, varying from a fibrillar to a homogeneous appearance, and varying in consistency from very dense and glassy in appearance, to the softer gelatinous substance between cells and around arteries and glands. This material increases with aging and eventually appears between cells in the muscular part of the uterus. With the injection of moderate amounts of estrogen, the quantity of the material is increased. When large amounts of estrogen are injected, "The connective tissue and muscle appear rarefied, almost as though they were perforated by a large number of small holes." "...this condition is presumably due to a deposit of a mixture of hyaline material and edematous fluid...." "This process of hyalinization...is counteracted by invasion by connective tissue." In this way there may take place in many areas a substitution and organization of the hyaline material by connective tissue, in which dilated capillaries may also be visible." "There is a second process which in many cases accompanies the invasion and organization of hyaline substance by connective tissue, namely a formation, at the margin of the hyaline material, of epithelioid and of small giant cells possessing more than one nucleus." "As a rule, the epithelioid cells are seen alone; giant cells are more rare." "...the connective-tissue fibrils may in places appear somewhat separated, perhaps by edematous fluid." "The first changes consist very likely in the transudation of fluid from the vessels into the connective tissue." "It seems, then, that at a very early stage after the beginning of the injections of effective doses of estrogen, a liquid substance which separates the connective-tissue elements makes its appearance, and that this represents one of the earliest changes induced by the hormone. It may be accompanied, or soon followed, by the deposit of a hyaline substance which occurs first between the connective-tissue cells, but may extend also to the muscle fibers." "...the deposit of hyaline which progressively becomes more and more devoid of connective-tissue cells and blood vessels, is so marked that the material acts like a foreign body...." "While it may be found also around blood vessels, such deposits are less conspicuous than in other organs in mice, such as the mammary gland.... There is a tendency for the hyaline substance to form sheaths around various organs and it is more prominent at the border separating different tissues and organs." "In its appearance and in the foreign body reactions which it initiates this substance somewhat resembles amyloid, which is readily produced in mice in various groups. The application of stains differentiating amyloid from other hyaline material, however, gave negative results."

Leo Loeb, V. Suntzeff, and E. L. Burns, "The effects of age and estrogen on the stroma of vagina, cervix and uterus in the mouse," Science 88(22, Nov. 4), 1938. "...large amounts of a hyaline substance are deposited, which act as foreign bodies and cause the formation of epithelioed and giant cells and an ingrowth of connective tissue. Thus an organization of this substance is attempted, which is interrupted, however, by renewed deposition of this hyaline material." "No definite statement can be made at present as to the chemical nature of this substance and its possible relation to a plasma constituent, except that it is not amyloid." "...a very intense fibrosis and hyalinization of the stroma which may induce abnormal reactions in the surrounding tissue. In this way it seems to be possible to accelerate and intensify very much some of the old age changes in certain organs."

Winfried G. Rossmanith, "Gonadotropin secretion during aging in women: Review article," Exp. Gerontology 30(3/4) 369-381, 1995. "...major functional derangements, primarily at a hypothalamic rather than a pituitary site, have been determined as concomitants of aging in women." "...aging may impair the negative feedback sensitivity to ovarian sex steroids...." Hormonal changes at menopause "may represent the sum of functional aberrations that were initiated much earlier in life...." "...prolonged estrogen exposure facilitates the loss of hypothalamic neurons...."

J. R. Brawer, et al., "Ovary-dependent degeneration in the hypothalamic arcuate nucleus," Endocrinology 107, 274-279, 1980.

G. C. Desjardins, "Estrogen-induced hypothalamic beta-endorphin neuron loss: A possible model of hypothalamic aging," Exp. Gerontology 30(3/4), 253-267, 1995. "This loss of opioid neurons is prevented by treatment with antioxidants indicating that it results from estradiol-induced formation of free radicals." "...this beta-endorphin cell loss is followed by a compensatory upregulation of mu opioid receptors in the vicinity of LHRH cell bodies." Resulting supersensitivity of the cells results "in chronic opioid suppression of the pattern of LHRH release, and subsequently that of LH." The neurotoxic effects of estradiol causes a "cascade of neuroendocrine aberrations resulting in anovulatory acyclicity." Treatment with an opiod antagonist "reversed the cystic morphology of ovaries and restored normal ovarian cycles" in estrogen-treated rats.

G. B. Melis, et al., "Evidence that estrogens inhibit LH secretion through opioids in postmenopausal women using naloxone," Neuroendocrinology 39, 60-63, 1984.

H. J. Sipe, et al., "The metabolism of 17 beta-estradiol by lactoperoxidase: A possible source of oxidative stress in breast cancer," Carcinogenesis 15(11), 2637-2643, 1994. "...molecular oxygen is consumed by a sequence of reactions initiated by the glutathione thiyl radical. ...the estradiol phenoxyl radical abstracts hydrogen from...NADH to generate the NAD radical." "...the futile metabolism of micromolar quantities of estradiol catalyzes the oxidation of much greater concentrations of biochemical reducing cofactors, such as glutathione and NADH, with hydrogen peroxide produced as a consequence."

S. Santagati, et al., "Estrogen receptor is expressed in different types of glial cells in culture," J. Neurochem. 63(6), 2058-2064, 1994. "...in all three types of glial cell analyzed in almost equal amounts..."

D. X. Liu and L. P. Li, "Prostaglandin F-2 alpha rises in response to hydroxyl radical generated in vivo," Free Radical Biol. Med. 18(3), 571-576, 1995. "Free radicals and some free fatty acids, such as arachidonic acid metabolites...may form a

feedback loop in which generation of one type leads to formation of the other." "Prostaglandin F-2 alpha dramatically increased in response to hydroxyl radical generation...."

J. Owens and P. A. Schwartzkroin, "Suppression of evoked IPSPs by arachidonic acid and prostaglandin F-2 alpha," Brain Res. 691(1-2), 223-228, 1995. "These findings suggest that high levels of AA and its metabolites may bias neurons towards excitation."

E. A. Quail and G. C. T. Yeoh, "The effect of iron status on glyceraldehyde 3-phosphate dehydrogenase expression in rat liver," FEBS Lett. 359(2-3), 126-128, 1995. "...the overexpression of GAPDH mRNA in iron deficiency is probably due to increased message stability." [This is one of the points discussed by Henics. Estrogen, which increases iron retention, also modifies mRNA stability.]

J. G. Liehr, et al., "4-hydroxylation of estradiol by human uterine myometrium and myoma microsomes: Implications for the mechanism of uterine tumorigenesis," Proc Natl Acad Sci USA 92(20), 9220-9224, 1995. "... elicits biological activities distinct from estradiol, most notably an oxidant stress response induced by free radicals generated by metabolic redox cycling reactions."

J. G. Liehr and D. Roy, "Free radical generation by redox cycling of estrogens," Free Rad. Biol. Med. 8, 415-423, 1990.

F. Fourrier, Circ. Shock 43(4), 171-178, 1994, "High estrogen levels were specifically observed in patients with sepsis and septic shock, either males or females." "Circulating T levels were decreased in all male patients."

J. A. Jarvis, et al., "H-1 NMR analysis of fibril-forming peptide fragments of transthyretin," Int. J. Pept. Protein Res. 44(4), 388-398, 1994. "...fragments of the protein transthyretin, previously shown to form cross beta-sheet amyloid-like fibrils in vitro, were investigated...."
