Ray Peat's Newsletter

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PREMISES FOR AN ARGUMENT:

Environmental factors, including polyunsaturated fats, exogenous estrogens, and heavy metals, and nutritional deficiencies, create an exaggerated estrogenic state, which synergizes with other intermittent stresses. These external stressors provoke the release of many kinds of stress mediating signal substances.

Aging is a progressive inflammatory state, in which there is an imbalance between excitatory and restorative processes, that progresses toward a shock-like state.

The antistress hormone, cortisol, causes tissue atrophy and cellular death in the process of resisting chronic stress.

Circulation and metabolism influence each other, with inflammation and shock, hypoxic metabolism and hypoperfusion promoting each other.

Inflammatory mediators damage mitochondrial respiration and cause cell swelling. Swelling impairs circulation and cell function.

Inflammatory autoimmune diseases and diabetes are much more common in women than in men. Insulin resistance appears at puberty, and diabetes is more common in girls than in boys. At menopause, 50% of women have distinct insulin resistance. Insulin resistance and the inflammatory autoimmune diseases are clearly promoted by estrogen.

The chronic increase of cortisol in response to stress increases estrogen.

Changing metabolism, producing lactate rather than carbon dioxide, changes the pH of the cell and its water content, allowing water-soluble metals to enter mitochondria.

Diabetes, neuropathies, myopathies, schizophrenias, the degenerative brain diseases, congestive heart failure, multiple organ failure, reduced lung function, insomnia, nocturnal cramps, and many other disorders have similar metabolic features, justifying similar therapies.

Estrogen, calcium, heavy metals, and nerve degeneration.

In the 1960s, someone noticed that a certain crease on the ear-lobe was a strong indicator of the tendency to have a heart attack. A little later, different researchers showed an association of wrinkled skin with smoking, and a strong association between the percentage of polyunsaturated oils in the diet and premature wrinkling. At the same time, people were demonstrating that many factors contributed to the stiffening of connective tissues, and to a generalized "fibrosis." Intuitively, everyone seems to know that the state of the skin is an indicator of general vitality or decrepitude. But the habit of thinking in terms of specific diseases, rather than general processes, has kept people from seeing that wrinkles, and other connective tissue changes, are deeply related to the major diseases of aging.

The senile brain accumulates a variety of mineral deposits, and the argument has been made that dietary aluminum is the cause of Alzheimer's disease. It would be good to eliminate added aluminum from our public water systems and from our foods, but there is good evidence that other processes are behind the accumulation of aluminum and other minerals in our tissues.

With aging, minerals such as calcium, iron, aluminum, cadmium, lead, mercury, fluoride, uranium, etc., accumulate in animal tissues, especially when those tissues are metabolically defective. But as the soft tissues mineralize, the bones and teeth demineralize. In both hard and soft tissues, mitochondria regulate mineralization.

Mercury has been used medically for a long time, and one of the popular uses for mercurial compounds has been as a diuretic. The mercurial

diuretics suppress the kidneys' respiratory activity and their ability to retain minerals, allowing fluids to pass through them relatively unconstrained. This led to the understanding that the mercury acted by interfering with the sulfhydryl groups (mostly the cysteines in proteins) in kidney cells, so when microscopic studies showed that the mercurial diuretic caused calcification, beginning in the mitochondria, this added to knowledge of how mitochondria work, as well as to the general process of soft tissue mineralization.

Hans Selye studied the process of metal-induced calcification in rats. In one group of experiments, he showed that an excess of iron causes calcification of areas of skin that have been slightly injured, for example by having the hair plucked. Treatment of the rats with vitamin E blocked the oxidative effects of iron and prevented calcification. Ordinary injuries, such as bruises, sometimes calcify, presumably under the influence of hemoglobin and iron.

Many toxins that oxidize the sulfhydryl (SH) groups in mitochondria synergize with calcium overload to produce metabolic inactivation of the mitochondria, usually accompanied by swelling. For many years it has been recognized that a practically instantaneous effect of estrogen is to cause cells to take up water. Its next step is to stimulate the synthesis of fats. Both of these processes involve pervasive changes in the energetic processes of the cells. Among the later changes produced by estrogen is increased collagen production.

It has long been recognized that injury or irritation is likely to lead to calcification, through the stages of inflammation, edema, and fibrosis, sometimes with fatty degeneration. These are the changes that led people to think of radiation damage as a form of accelerated aging. X-ray treatment commonly causes calcification of important organs such as the brain and the heart, though skin calcification was among the first radiation side-effects noticed. After 100 years of relative scientific inertia, there has recently been some progress in understanding the common processes behind "injury induced mineralization."

The biochemical arguments in the next few paragraphs simply outline some of the facts that have been omitted from the mainstream discussions of brain aging, estrogen, and mineralization.

When I began studying the physiology of estrogen, I found that the biochemical changes it caused were the same as those of aging, oxygen-deprivation, and radiation injury.

In my experiments, I found that both aging and estrogen stimulation caused a great increase in the availability of reactive electrons, which I measured by their reaction with a dye. These electrons come from an interactive system that involves the proteins (cysteine) and glutathione, and the various cofactor-catalysts such as ascorbic acid and NADH (NAD is nicotinamide adenine dinucleotide; the name reveals its connections to the vitamin, niacin/nicotinamide, and to the "energy molecule," ATP, adenosine triphosphate, but biochemists are seldom concerned with those links; the H indicates the reduced, electronically energized form of the molecule).

Glutathione and other antioxidants tend to prevent oxidative damage to the mitochondria's sulfhydryl groups. Simply lowering the pH is highly protective against oxidative attack by metals, and this is partly because the electrons of the sulfhydryl groups are less accessible to the oxidants in an acidic environment. The formation of carbon dioxide is the fundamental process for keeping mitochondrial pH low.

Glutathione depends on being regenerated by the reducing molecule, NADH. When NADH is consumed elsewhere at a high rate, glutathione itself becomes oxidized and unable to protect the mitochondria, and the consumption of NADH (as in the formation of lactic acid) tends to consume protons, raising the pH. So the rate at which NADH is consumed can be crucial in the life and health of a cell. NAD is so closely related to the availability of ATP that the cell death system can be triggered by a deficiency of NAD (Catisti, et al., 1999).

The cell's reductive system, centering on NADH and NADPH (the extra P, phosphate, in this molecule allows it to be regulated separately from NAD), is closely involved in fat synthesis. If estrogen serves as a redox (reduction and oxidation) link between NADH and NADP, fat

synthesis will be an additional drain on the available NADH.

In the 1950s, several endocrinologists gathered evidence to show that estrogen can function as a catalyst in the oxidation and reduction of the pyridine nucleotides, NADPH and NADH. But in the 1960s, the doctrine that estrogen's effects were mediated exclusively by the "estrogen receptor" began replacing all other ideas about estrogen chemistry and physiology.

J. G. Liehr, and a few others, are still demonstrating that estrogen can function as a catalyst in "redox cycling" (alternate reduction and oxidation), which generates toxic free radicals, and can potentially serve as a drain on the NADH systems. In functioning as a redox catalyst, estrogen oscillates between an oxidized and a reduced molecular form. In this context, the ratio of the different forms of estrogen takes on an entirely different meaning than simply their different effects on the so-called estrogen receptors. Since the doctrine of the estrogen receptor became a medical preoccupation, most attention has been given to estradiol, since it is the "strongest" estrogen in some tests, though estrone, the oxidized form, is usually present in the blood in much larger quantities. The quantity of the oxidized form of estrogen is increased in certain degenerative conditions, such as uterine cancer, which is a strong argument against the idea that, as a "weaker estrogen," it would moderate the effect of estradiol.

In my dissertation, I gave a few other arguments regarding the wasteful consumption of NADH. There is now good evidence for the existence of estrogen-stimulated extramitochondrial NADH oxidases, in addition to the NADH oxidase function of age pigment, that I have discussed in an earlier newsletter.

Until the late 1970s, the fact that estrogen causes increased absorption of calcium was offered as proof that it prevents osteoporosis, but then it turned out that the increased retention of calcium was occurring ***only in the soft tissues,*** where calcification is a normal trend with aging. In fact, bone loss begins in a woman's twenties, and continues fairly steadily during the period in which the actual level of estrogen is rising.

Arteries and tendons tend to calcify with aging, the brain and pineal gland, kidneys and other organs retain more calcium and gradually lose functions, and cells die with a calcium overload.

Estrogen's stimulation of iron absorption was ignored by people who wanted to sell iron pills (often 18 mg per day) to women who lost iron (maybe 5 mg per month) by menstruation. After menopause, women absorb iron so fast that their body's iron load generally catches up with men's within a few years, at which time their incidence of heart attacks becomes similar to men's. If estrogen is a major factor in the promotion of iron absorption, **women's accelerated iron retention after menopause argues for the existence of a *more estrogenic state than when they were younger.*** Since progesterone falls sharply at menopause, the effect of the unopposed estrogen is going to be very strong, even as the absolute quantities of estrogen are declining.

When progesterone falls, the effects of cortisol, as well as estrogen, are increased, because progesterone antagonizes both of those hormones. Under the influence of cortisol, fat cells produce estrogen, and this effect is normally inhibited by progesterone and thyroid.

Calcification of soft tissues and iron retention accelerate at menopause. The body accumulates calcium, but it isn't going into the bones. The body accumulates iron, and it too goes into the soft tissues. Increased iron storage in the liver is associated with insulin resistance, and increased iron in any tissue is associated with increased lipid peroxidation in stress.

Calcium and iron tend to be deposited together, and the mitochondria are usually the starting points for their deposition. Iron overload has been implicated in heart disease, cancer, diabetes, and many other degenerative diseases, including the brain diseases.

Estrogen, and the free fatty acids that are liberated under its influence, increase the permeability of blood vessels, allowing water, proteins, etc., to leak out into the tissues. Tumor necrosis factor, induced by estrogen, reduces the "blood

brain barrier" function, promoting brain inflammation. The "blood brain barrier" means that water soluble molecules are excluded, while oil soluble molecules enter freely. Highly charged particles such as metal ions are normally efficiently excluded from the brain, in proportion to their water-solubility..

The free unsaturated fatty acids associated with estrogen's influence cause brain edema and mitochondrial damage (Catisti, et al., 1999). Although the fatty acids enter cells and mitochondria easily because the cytoplasm and mitochondria are lipophilic, unsaturation of a fat makes it a little less fat soluble, and more water soluble. Unsaturation also makes the fat more likely to be oxidized into toxic products, and to damage the mitochondria, suppressing its respiration, and forcing the cell into the less efficient glycolytic metabolism, raising the cell's pH, which makes the cell take up more water.

All of the biochemical features of Alzheimer's disease are consistent with prolonged estrogen excess. Estrogen's toxicity to the developing brain was established in the 1950s and 1960s. Maybe it's a kind of progress, that the claimed benefits of estrogen have aged with the drug industry: in 1940 estrogen helped you get pregnant, in 1950 it helped you to maintain pregnancy, in 1960 it helped to prevent or interrupt pregnancy, in 1970 it helped you retain calcium and iron to build strong bones and blood, in 1960 and 1990 it helped prevent heart attacks, and now finally it has nothing left to do but to prevent senile dementia.

The virologist, Gajdusek, wanted to argue that his virus, and not the accumulation of aluminum, was responsible for kuru and other brain degenerative diseases, and so he did a survey of brains of demented people from regions with different types of soil, and showed that the most abundant metals in the environment showed up in the brains. He argued that this showed that the metal deposition was just the consequence of a viral disease, rather than the cause of the brain degeneration. He observed that the deposits consisted mainly of calcium in regions that didn't have large amounts of other metals, so he argued that a particular metal such as aluminum couldn't be responsible for brain degeneration. But he didn't consider that factors other than viruses might be responsible for the brain mineralization that he saw.

Although women have more osteoporosis and more Alzheimer's disease than men do, the *lack* of estrogen is currently blamed for both of the problems. Why would Alzheimer's disease be so different from the other predominantly female diseases that have been linked to excess estrogen? Why would women's brains be different from men's? Why would their nerve cells degenerate without estrogen, while men's don't? Obviously women's brains and nerves aren't very different from men's and there simply isn't any sensible reason to believe that "estrogen deficiency" is responsible for Alzheimer's disease, or for osteoporosis, or for heart disease, or any of the other problems that have been blamed on the "menopausal estrogen deficiency."

The mass media find and publicize the things they want to believe, or want the public to believe. "Coffee causes heart disease," "estrogen prevents Alzheimer's disease," they say. How do they make the argument? Using plausible sounding terms that hide the real situation is the general technique. I don't want to give science reporters disproportionate blame, because specious argumentation is habitually practiced by many of the professors and researchers who provide the raw material for the news reports. In literature, "poetic diction" is intended to put the reader into a certain frame of mind, to be receptive to the poet's purpose. Many scientists rely on something like "poetic diction."

For example, a San Francisco study by Kristine Yaffe and co-authors found that "free estrogen," "the active form of the hormone," was higher in more of the people who had better cognitive function. Yaffe, et al., also found that dementia is associated with both depression and osteoporosis.

There isn't really such a thing as "free estrogen," which is defined in terms of a particular laboratory situation that doesn't correspond to anything in the body. Estrogen is insoluble in water, unless there is a large amount of alcohol present as solvent. When solids are present in a solution, estrogen passes directly from one solid to another, according to the momentary properties

of the solids. The laboratory measurement of "free estrogen" is describing both a physiological and a physical fantasy.

"Protein bound estrogen" is an active form of estrogen, and the estrogen bound to albumin probably accounts for most of estrogen's activity. Free fatty acids, which compete with estrogen for binding to the steroid-binding globulin, probably modify the properties of the more abundant albumin so that it binds more estrogen in its active form, causing estrogen to move from other proteins, lipoproteins, and red blood cells onto the activated albumin. **The presence of fats bound to the albumin makes the albumin more lipophilic, fat-loving, and molecules are taken up into cells--especially brain cells--according to their solubility in fats. For fatty molecules, there is no "blood brain barrier."** The fact that albumin has variable lipophilicity makes it an effective mechanism for the transport and delivery of oil soluble molecules.

Yaffe, et al., in associating depression and osteoporosis with dementia, are arguing that estrogen deficiency is the cause of all three conditions. They offer some hypothetical mechanisms for how estrogen might prevent Alzheimer's disease. Observing that brain cells die in people with Alzheimer's disease, they mention that estrogen stimulates "dendritic sprouting" in brain cells, as if that could compensate for the loss of cells (it doesn't). They observe that estrogen delivers more tryptophan to the brain, increasing the production of serotonin, and that it inhibits the monoamine oxidases and other enzymes that inactivate transmitter substances, increasing the activity of adrenaline, serotonin, and other transmitter substances. They suggest that increased circulation caused by estrogen might protect the brain. Here, Yaffe, et al., have invoked **the serotonin myth and other myths, including the nitric oxide myth, to substantiate the estrogen myth.**

Serotonin doesn't "cure depression," and both serotonin and nitric oxide impair circulation and are toxic to brain cells. Both of them poison mitochondrial respiration. Estrogen increases the viscosity of blood, and impairs circulation and oxygenation in many other ways.

The actual level of estrogen rises all through the reproductive years, and at menopause, the reduction in antiestrogenic factors, such as progesterone, thyroid, and DHEA, leads to increased effects of estrogen. The increased burden of unsaturated fatty acids that accumulate with aging clearly promotes the effects of estrogen and interferes with the production of the antiestrogenic hormones. These unsaturated fats cause progressive slowing of the metabolic rate, with particularly sharp decreases around puberty and menopause. As they interfere with the production of energy, they tend to increase cellular energy requirements, by promoting excitatory cellular processes.

Estrogen and PUFA create insulin resistance, and the resulting state of "diabetes" and stress de-energizes tissues, with the mitochondria that are damaged by unsaturated fatty acids, nitric oxide, tumor necrosis factor (TNT), serotonin, etc., failing to meet the tissues' energy needs. Stress, endotoxinemia, and increased estrogen tend to activate TNF, which has a role in brain degenerative diseases and osteoporosis and multiple organ failure. Much research has focussed on a search for a single substance that is responsible for the inflammatory conditions of Alzheimer's disease, but inflammation and aging are processes that involve many causes and mediators, with each individual's history causing variations in the details.

"Diabetes," or the inability to oxidize glucose vigorously, is simply a description of the metabolic aspect of cellular degeneration. The neurological impairment that is so commonly associated with officially diagnosed diabetes is simply one aspect of a general cellular malfunction that follows from chronic energy deprivation. Exactly the same processes occur in the sudden organ failure produced by shock, or the gradual organ failures--lungs, liver, kidney, heart, thymus, brain--that occur in aging. In general, there is a failure of circulation that exacerbates the metabolic and functional failures.

Diabetes, of both the insulin dependent and the non-insulin dependent types, is commonly associated with increased cortisol. In diabetes, inflammatory conditions, and under the influence

of increased cortisol, brain cells are deprived of glucose.

Increased cortisol is a normal response to the cell-damaging effects of stress or inflammation, but cortisol itself causes the death of nerve cells and immune cells through excitotoxicity, by blocking glucose metabolism. Estrogen increases cortisol production in a variety of ways, acting both through the pituitary and directly on the adrenal glands. Estrogen promotes excitotoxic processes, by opposing progesterone and thyroid, by directly exciting nerve cells, and by increasing the activity of excitatory nerve transmitters. It also increases serotonin, which blocks energy production by its effect on mitochondria, as well as by impairing circulation..

At puberty, there is a sudden increase in the incidence of depression, especially in girls. Increased adrenaline, like increased cortisol, is a feature of depression, stress, and inflammation; mobilizing fats, it can become part of a vicious circle, in which free fatty acids cause insulin resistance, activating the stress reactions. Increased serotonin is a feature of inflammation, shock, stress, and depression, and, like histamine, is tied very closely to estrogen's effects.

Estrogen does have some of the effects mention by Yaffe, et al., but these effects should make a person wonder whether estrogen isn't an important factor in the development of Alzheimer's disease, rather than being its main preventive agent.

In Alzheimer's disease, there is a distinct decrease in blood pressure, and orthostatic hypotension is a common feature of dementia. Estrogen's relaxing effect on the blood vessels has been shown to allow blood pooling in the veins, producing orthostatic hypotension. Estrogen, acting directly and through mediators such as serotonin, decreases the heart's pumping efficiency.

Blood viscosity is increased in Alzheimer's disease, and estrogen is known to increase blood viscosity.

Nitric oxide, a third cultic substance along with serotonin and estrogen, is invoked as a normalizer of brain circulation and protector of nerve cells from peroxidation. Whether a substance is an antioxidant or pro-oxidant depends on its environment, and both nitric oxide and estrogen are pro-oxidants, promoters of lipid peroxidation and other forms of cell damage, under a variety of physiological situations.

If authors are criticizing a well known doctrine, it is reasonable for them to assume that their readers know the arguments in favor of that doctrine, and to concentrate on their critical points. But Yaffe, et al., are arguing *in favor* of a well known doctrine. They fail to present the actual research situation. For them to ignore the work of people like Brawer, Desjardins, Schipper, and Liehr, who have explored the cytotoxic and neurotoxic effects of estrogen, amounts to simple propaganda. When such material is published in the mass media, such as JAMA, its effect can be considered as equivalent to fraud, since these media don't publicize alternative views.

While there has been some publicity about a recent study that found that treating Alzheimer's patients with estrogen for 12 weeks didn't improve their mood or mental ability, there has been relative silence about all the studies that show actual deterioration of mentality or mood in association with increased estrogen.

In old men, higher estrogen was found to be associated with lower mental ability (Barret-Connor, et al., 1999). Although estradiol is the most potent estrogen, estrone is the main estrogen in the circulation in terms of its quantity, and women's mental performance was found to be lower when the estrone was higher (Yaffe, et al., 1998).

Antiendorphin, antiexcitotoxic, anticholinergic, antiserotonergic, antiprostaglandin, and antiglucocorticoid drugs have been used with good effect in various degenerative nervous diseases, but all the so-called "anti" drugs are imprecise antagonists, and have many side effects. The natural antagonists and nutrients are usually helpful. Protein, sodium, magnesium, carbon dioxide/bicarbonate, progesterone, thyroid, vitamins, etc., can be curative in many brain diseases, but are seldom tried because of cultic medical ideas about nutrition, hormone tests, and the nature of cells and disease.

To the extent that unsaturated fats, heavy metals, and estrogenic substances (such as soybean products; tofu, for example, was recently implicated in dementia) can be avoided, the interactive processes of cell damage can be retarded. Natural restorative processes can maintain tissue integrity if the destructive processes are slowed.

REFERENCES

Neurology 2000 Jun 13;54(11):2061-6. **Effects of estrogen on cognition, mood, and cerebral blood flow in AD: a controlled study.** Wang PN, Liao SQ, Liu RS, Liu CY, Chao HT, Lu SR, Yu HY, Wang SJ, Liu HC. "CONCLUSION: A 1.25-mg/day dose of Premarin administered for 12 consecutive weeks does not produce a meaningful effect on cognitive performance, dementia severity, behavior, mood, and cerebral perfusion in female AD patients. Because estrogen therapy has been suspected of yielding adverse effects, and its therapeutic effectiveness is in doubt, additional evaluation of its role in AD treatment ought to be conducted."

J Clin Endocrinol Metab 1999 Oct;84(10):3681-5. **Endogenous sex hormones and cognitive function in older men.** Barrett-Connor E, Goodman-Gruen D, Patay B. ."In age- and education-adjusted analyses, **men with higher levels of total and bioavailable estradiol had poorer scores on the BIMC Test and Mini-Mental State Examination**. Men with higher levels of bioavailable testosterone had better scores on the BIMC Test and the Selective Reminding Test (long-term storage)." "All associations were relatively weak but independent of age, education, body mass index, alcohol use, cigarette smoking and depression. **In these older men, low estradiol and high testosterone levels predicted better performance on several tests of cognitive function.** Linear and nonlinear associations were also found, suggesting that an optimal level of sex hormones may exist for some cognitive functions."

J Am Geriatr Soc 1998 Jul;46(7):816-21. **Serum estrogen levels, cognitive performance, and risk of cognitive decline in older community women.** Yaffe K, Grady D, Pressman A, Cummings S. **"Women in the higher estrone quartiles had 15% lower (worse) scores on Digit Symbol** compared with the lower quartiles (P=.004) but there was no difference by quartile on the modified MMSE or on Trails B. Cognitive function test scores declined over the 5 years of follow-up. There was no difference in amount of change by quartile of estradiol, **but women in the higher estrone quartiles had greater reduction of scores on Trails B compared with those in the lower quartiles (P=.012), even after adjusting for age, education, depression, stroke history, weight, and change in weight** since age 50. The age-adjusted odds of cognitive decline (defined as tenth percentile of women with the largest decline in cognitive performance) did not vary across quartile of estrone or estradiol. CONCLUSIONS: Endogenous estrogens are not associated consistently with cognitive performance or risk of cognitive decline on a selected battery of cognitive tests in older community-dwelling women. **Worse performance on two cognitive tests among women with higher estrone levels was surprising and warrants further investigation."**

FEBS Lett 1999 Dec 24;464(1-2):97-101. **The participation of pyridine nucleotides redox state and reactive oxygen in the fatty acid-induced permeability transition in rat liver mitochondria.** Catisti R, Vercesi AE. "Here, we have compared the PTP opening ability of arachidonic acid (AA) with that of carbonyl cyanide-p- rifluoromethoxyphenylhydrazone (FCCP) at concentrations that cause similar quantitative dissipation of the membrane potential (DeltaPsi) in Ca(2+)-loaded rat liver mitochondria respiring on succinate." "This second phase of DeltaPsi dissipation could also be prevented by rotenone or NAD(P)H-linked substrates which decrease the pyridine nucleotide (PN) oxidation that follows the stimulation of oxygen consumption induced by AA or FCCP. These results suggest that, under the experimental conditions used here, the PTP opening induced by AA or FCCP was a consequence of PN oxidation. Exogenous catalase also inhibited both AA- and FCCP-induced PTP opening. These results indicate that a condition of oxidative stress associated with the oxidized state of PN underlies membrane protein thiol oxidation and PTP opening."

FEBS Lett 2000 Jul 28;478(1-2):29-33. **The redox state of endogenous pyridine nucleotides can determine both the degree of mitochondrial oxidative stress and the solute selectivity of the permeability transition pore.** Zago EB, Castilho RF, Vercesi AE. "We propose that the shift from a low to a high conductance state of the PTP can be promoted

by the oxidation of NADPH. This impairs the antioxidant function of the glutathione reductase/peroxidase system, strongly strengthening the state of mitochondrial oxidative stress."

J Neurosci Res 2000 Sep 1;61(5):570-575. **Endogenous generation of cyanide in neuronal tissue: Involvement of a peroxidase system.** Gunasekar PG, Borowitz JL, Turek JJ, Van Horn DA, Isom GE.

Biochem Mol Med 1995 Feb;54(1):1-11. **Proposed role for a combination of citric acid and ascorbic acid in the production of dietary iron overload: a fundamental cause of disease.** Crawford RD. "This paper presents a review of the significant body of literature liking **dietary iron overload, not only to heart disease, but also to cancer, diabetes, osteoporosis, arthritis, and possibly other disorders."**

Cancer Res 1995 Apr 15;55(8):1664-9. **Effect of estrogen withdrawal on energy-rich phosphates and prediction of estrogen dependence monitored by in vivo 31P magnetic resonance spectroscopy of four human breast cancer xenografts.** Kristensen CA, Kristjansen PE, Brunner N, Clarke R, Spang-Thomsen M, Quistorff B. "Estrogen **withdrawal induced a significant increase in the nucleoside triphosphate:Pi ratio in the two estrogen-dependent xenografts, whereas this ratio remained** unchanged in the estrogen-independent tumors." [Tumor growth was inhibited, and the ATP increased.]

Carcinogenesis 1998 Jul; 19(7):1285-90. **Enhancement of estrogen-induced renal tumorigenesis in hamsters by dietary iron.** Wyllie S, Liehr JG. Iron participates in the generation of hydroxyl radicals by the iron-catalyzed Fenton reaction. Its role in estrogen-induced carcinogenesis has been examined in this study by investigating the effects of iron content of hamster diets on tumor induction by estradiol. The renal tumor incidence and number of tumor nodules in hamsters treated with estradiol plus a diet enriched with iron (384 p.p.m. Fe as ferric citrate) for 5 months were 2- and 4-fold higher, respectively, than those observed in animals on an iron-poor diet plus estradiol (3.9 p.p.m. Fe, as ferric citrate). Tumor incidence and number of tumor nodules in estradiol-treated hamsters on the iron-deficient diet were not different from those of animals on a normal rodent chow. No tumors were detected in hamsters treated only with the low or high iron diets. Total serum iron was significantly increased in animals treated with the high iron diet plus estradiol compared with the low iron diet plus estradiol group and the high and low iron controls. Estrogen treatment increased non-heme iron in liver of both high and low iron treatment groups and in kidney of the hamsters on the low iron diet. It is concluded that dietary iron enrichment enhances the incidence and severity of estrogen-induced tumor induction.

Annu Rev Nutr 1997;17:37-50. **Toxic and essential metal interactions.** Goyer RA. Cadmium, lead, mercury, and aluminum are toxic metals that may interact metabolically with nutritionally essential metals. Iron deficiency increases absorption of cadmium, lead, and aluminum. Lead interacts with calcium in the nervous system to impair cognitive development. Cadmium and aluminum interact with calcium in the skeletal system to produce osteodystrophies. Lead replaces zinc on heme enzymes and cadmium replaces zinc on metallothionein. Selenium protects from mercury and methylmercury toxicity. Aluminum interacts with calcium in bone and kidneys, resulting in aluminum osteodystrophy. **Calcium deficiency along with low dietary magnesium may contribute to aluminum-induced degenerative nervous disease.**

Mech Ageing Dev 1998 May 1;102(1):1-13. **Iron accumulation in aging: modulation by dietary restriction.** Cook CI, Yu BP. "Male Fischer 344 rats fed ad libitum or dietary restricted (maintained on 60% of ad libitum food intake) were sacrificed at 6, 12 and 24 months of age." "Tissue total iron content was shown to increase significantly with age in animals fed ad libitum (AL). At 24 months, these animals showed comparable iron content increases in the liver and kidney, but were significantly greater than measurements found in brain. This age-related iron accumulation, however, was found to be markedly suppressed by dietary restriction (DR) in all tissues. Similarly, LPO measurements increased in an age-related, tissue-specific fashion. **At 24 months of age, measurements of LPO in AL rats brain and liver exceeded measurements in kidney. Again, we found DR to markedly suppress age-related LPO in all tissues.** Reported here are our findings on the ability of DR to modulate iron status at the tissue level. Consistent with the proposed anti-oxidative mechanism of DR, these findings further suggest that the modulation of tissue total iron content is an important component of that mechanism.

. Age 17(3), 93-97, 1994. **Modification of age-related alterations of iron, ferritin, and lipid peroxidation in rat serum.** Choi, JH and Yu, BP.