A R T I C L E

Vitamin E: Estrogen antagonist, energy promoter, and anti-inflammatory

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Vitamin E, like progesterone and aspirin, acts within the cellular regulatory systems, to prevent inflammation and inappropriate excitation. Since uncontrolled excitation causes destructive oxidations, these substances prevent those forms of oxidation.

Molecules that can easily be oxidized and reduced can function as antioxidants, and vitamin E does function as that kind of antioxidant in many chemical environments. But it is highly misleading to consider that as the explanation for its many beneficial biological effects. That kind of reasoning contributed to the use of the antioxidant carcinogens BHT and BHA as food additives and "antiaging" supplements, and many other chemicals are being promoted on the basis of their abstract antioxidant function.

Becoming aware of the real value of vitamin E will have far reaching implications in nutrition and medicine.

In determining criminal or civil legal responsibility, the concept "should have known" is recognized and used. In science, which is all about knowing, there is certainly a responsibility to be informed when the subject involves the life and health of millions of people. The science establishment of government and industry should be held responsible for the information it hides, destroys, or ignores for its own benefit. The US government has an agency for prosecuting research fraud, but the concept is applied so narrowly as to be meaningless, when deception has become the rule. And since it controls the court system, govenment agencies and their functionaries won't be prosecuted, even when their crimes become well known.

"*Vitamin E was advocated as an effective treatment for heart disease by Dr. Evan Shute of London, Ontario more than 50 years ago. His pioneering claims, which were unacceptable to the medical community at large, have been confirmed by recent findings from epidemiologic studies and clinical trials.*"

Political scientists have recognized the process in which big corporations "capture" the governmental agencies that were created to regulate them. The editorial boards of professional journals can be captured even more cheaply than the agencies of government, and their influence can be even more valuable to industry.

If science impinges upon the plans of an industry, it can be managed into compliance, when the industry controls the journals and the agencies that fund research.

In the 1940s, it had already become clear to the estrogen industry that vitamin E research was impinging on its vital interests.

The Manhattan Project, that created the atomic bomb, also created a generation of scientific and bureaucratic zealots who ignored public health and safety to advance their projects and their careers, and changed the way science was done. At exactly the same time, the pharmaceutical industry was using its financial and political power to change the way medicine was practiced and taught, and the consequences for world health rivalled those of the nuclear industry.

In 1933 the physician R.J. Shute was aware of the problems associated with toxemia of pregnancy or preeclampsia. Especially among poorly nourished women, many pregnancies were complicated by circulatory problems, including cyclic bleeding, thrombosis, stroke, and hypertension, and these difficult pregnancies often ended in miscarriage or premature delivery, resulting in many serious health problems among

the babies that survived.

At that time, both estrogen and vitamin E were being widely studied, though the exact structure of the tocopherol molecule wasn't defined until 1936-37. Vitamin E had been found to improve fertility of both male and female animals, and to prevent intrauterine death of the embryo or fetus, so it was called the "antisterility vitamin." Using it to prevent women from having miscarriages must have occurred to many people.

Animal research in the 1930s was also showing that estrogen had many toxic effects, including causing infertility or intrauterine death, connective tissue abnormalities, and excessive blood clotting. Dr. Shute and his sons, Wilfred and Evan, were among those who considered vitamin E to be an antiestrogen. They found that it was very effective in preventing the clotting diseases of pregnancy.

Other researchers, who knew that progesterone protected against the toxic effects of estrogen, described vitamin E as the "progesterone-sparing agent," since so many of its antiestrogenic effects resembled those of progesterone.

The Shute brothers began using vitamin E to treat circulatory diseases in general, rather than just in pregnant women--blood clots, phlebitis, hypertension, heart disease, and diabetes all responded well to treatment with large doses.

Vitamin E, as its name indicates, was the fifth type of "vitamin" factor to be identified, and it received its name in 1922, even though its chemical structure hadn't been identified. The public quickly understood and accepted that certain substances in food were essential for life and health, so by 1940 practically all physicians were recommending the use of nutritional supplements.

If vitamin E was essential for human health, and achieved at least some of its amazing effects by opposing estrogen, then the synthetic estrogen industry had a problem.

Edward L. Bernays had already been in business for decades, teaching corporations and governments how to "engineer consent." After his work for the government to engineer support for entering the first world war, Bernays' next big job was for the tobacco industry. To convince women to smoke cigarettes, to achieve equality with men, he organized an Easter parade, Torches of Freedom, in which thousands of women marched smoking their freedom torches. In association with the American Medical Association (the editor of JAMA actually helped the tobacco industry design its campaigns), Bernays ran a campaign to convince Americans that smoking was good for the health.

The drug industry began using his techniques in sometimes crude but always effective ways. Estrogen was named "the female hormone;" natural hormones, including estrogen and progesterone, were claimed, without any research, to be inactive when taken orally. Physician-shills were created to claim wonderful effects for estrogen. The vitamin status of the tocopherols was denied; as recently as the 1970s (and maybe later), university professors of dietetics were flatly saying "no one needs vitamin E."

Very little research showing the curative effects of vitamin E in human diseases was allowed to be published, so it was only occasionally necessary to openly denounce vitamin E as worthless or dangerous. In 1981, the journal of the AMA published an article reviewing the "toxic" effects of vitamin E. Since I had read all of the articles cited, I realized that the author was claiming that whenever vitamin E changed something, the change was harmful, even though the original publication had described the effect as beneficial.

Although JAMA was eventually forced to give up its revenue from cigarette advertising, it didn't suffer at all, because of the vast advertising campaigns of the estrogen industry. JAMA obviously wouldn't want to publish anything suggesting that vitamin E, or progesterone, or thyroid, might be beneficial because of its antagonism of the harmful effects of estrogen.

Estrogen causes changes in the uterus that prevent implantation of the embryo, and that impair support for its development if it has already implanted. It decreases the availability of oxygen to the embryo, while

vitamin E increases it.

My dissertation adviser, A.L. Soderwall, did a series of experiments in which he showed that providing hamsters with extra vitamin E postponed the onset of infertility in middle age. In my experiments, vitamin E increased the amount of oxygen in the uterus, correcting an oxygen deficiency produced either by supplemental estrogen or by old age. Progesterone has similar effects on the delivery of oxygen to the uterus.

In the 1940s, the official definition of vitamin E's activity was changed. Instead of its effectiveness in preventing the death and resorption of embryos, or the degeneration of the testicles or brain or muscles, it was redefined as an antioxidant, preventing the oxidation of unsaturated oils.

Although some people continued to think of it as a protective factor against thrombosis, heart attacks, diabetes, and infertility, the medical establishment claimed that the prevention or cure of diseases in animals wasn't relevant to humans, and that a mere antioxidant couldn't prevent or cure any human disease.

The experiments that led to the identification of vitamin E involved feeding rats a diet containing rancid lard and, as a vitamin A supplement, cod liver oil. Both of these contained large amounts of polyunsaturated oils.

From 1929 to the early 1930s, other researchers were claiming to have demonstrated that the polyunsaturated fatty acids were nutritionally essential. These experiments, like the vitamin E experiments, were done on rats, but the medical establishment was satisfied that rat experiments proved that humans need linoleic or linolenic acid, while they refused to accept that vitamin E was essential for humans. When, in the 1940s, a group of vitamin B6 researchers showed that the supposed "essential fatty acid deficiency" could be cured by a supplement of vitamin B6, it became apparent that the polyunsaturated fatty acids slowed metabolism, and reduced all nutritional needs. The thyroid hormone was powerfully suppressed by the "essential" fatty acids.

When we consider the two sets of experiments together, their outstanding feature is the toxicity of the polyunsaturated oils, which in one kind of experiment suppressed metabolism, and in the other kind of experiment created a variety of degenerative conditions.

By the late 1940s and early 1950s, estrogens of various sorts had been synthesized from hydrocarbons, and were being recommended to prevent miscarriages, because "estrogen is the female hormone." The meat industry had found that the polyunsaturated oils were valuable in animal feed, since they suppressed metabolism and made it cheaper to fatten the animals, and these antithyroid oils were next marketed as "heart protective" human foods, though by suppressing the thyroid and destroying vitamin E, they actually contributed to both heart disease and cancer. (Giving estrogen to livestock to improve their feed efficiency, and to people "to prevent heart attacks," was an interesting parallel to the oil promotional campaigns.)

The influence of the food oil industry kept researchers away from the idea that these oils were not safe for food use, and instead tended to support the idea that vitamin E is just an antioxidant, and that the seed oils were the best way to get vitamin E in the diet.

The antifertility effects of the polyunsaturated oils, demonstrated in the vitamin E experiments, weren't at the time understood to have anything to do with estrogen's antifertility effects. But to understand vitamin E, I think we have to consider the close interactions between estrogen and the polyunsatured fatty acids (PUFA). Their actions are closely intertwined, and are antagonized by a variety of energizing and stabiliizing substances, including saturated fats, progesterone, thyroid, vitamin E, and aspirin.

Generally, chemicals that inhibit enzymes are toxic, producing some sort of symptom or deterioration. But a group of enzymes related to estrogen and PUFA are inhibited by these protective substances. Although under our present diet, these enzymes metabolize the PUFA, in the fetus and newborn they act on our endogenous fats, the series related to the Mead acids. The Mead acid is antiinflammatory, and broadly protective. The dietary PUFA interfere with these natural protective substances,

The enzymes that, if we didn't eat PUFA, would be regulating the Mead series, being activated in response to stress, would be producing antistress substances, which would limit the stress reaction. But as we become increasingly saturated with the anti-vitamin E fats, these enzymes, instead of stopping inflammation, promote it and cause tissue injury. The remaining stress limiting factors, such as progesterone, by correcting the distortions caused by stress, tend to eliminate the conditions which activated the enzymes--in a very indirect form of inhibition.

Many of the events involved in inflammation are increased by estrogen, and decreased by vitamin E. Estrogen causes capillaries to become leaky; vitamin E does the opposite. Estrogen increases platelet aggregation, and decreases a factor that inhibits platelet aggregation; vitamin E does the opposite.

Excess clotting is known to be caused by too much estrogen, and also by a vitamin E deficiency.

Clotting leads to fibrosis, and there is clear evidence that vitamin E prevents and cures fibrotic diseases, but this still isn't generally accepted by the powerful medical institutions. Estrogen and polyunsaturated fats increase fibrosis.

Estrogen increases progstaglandin synthesis, vitamin E decreases their synthesis; estrogen increases the activity of the enzymes COX and LOX, vitamin E decreases their activitiy. (Jiang, et al., 2000; Ali, et al., 1980; Parkhomets, et al., 2001.) Estrogen releases enzymes from lysosomes, vitamin E inhibits their release. Beta-glucuronidase, one of these enzymes, can release estrogen at the site of an inflammation.

Estrogen often increases intracellular calcium and protein kinase C, vitamin E has generally opposite effects.

The polyunsaturated fatty acids and their derivatives, the prostaglandins, act as effectors, or amplifiers, of estrogen's actions.

If vitamin E is acting as a protectant against the polyunsaturated fatty acids, that in itself would account for at least some of its antiestrogenic effects.

Besides antagonizing some of the end effects of the toxic fatty acids, vitamin E inhibits lipolysis, lowering the concentration of free fatty acids (the opposite of estrogen's effect), and it also binds to, and inactivates, free fatty acids. The long saturated carbon chain is very important for its full functioning, and this saturated chain might allow it to serve as a substitute for the omega -9 fats, from which the Mead acid is formed. The unsaturated tocotrienols have hardly been tested for the spectrum of true vitamin E activity, and animal studies have suggested that it may be toxic, since it caused liver enlargement.

One possibly crucial protective effect of vitamin E against the polyunsaturated fatty acids that hasn't been explored is the direct destruction of linolenic and linoleic acid. It is known that **bacterial vitamin E is involved in the saturation of unsaturated fatty acids, and it is also known that intestinal bacteria turn linoleic and linolenic acids into the fully saturated stearic acid.**

"No metabolic function is known for alpha-tocopherolquinol or its quinone other than as a cofactor in the biohydrogenation of unsaturated fatty acids that can be carried out by only a few organisms."

P.E. Hughes and S.B. Tove, 1982.

"Linoleic acid was significantly decreased (P < 0.001) and there was a significant rise (P < 0.05) in its hydrogenation product, stearic acid. Linolenic acid was also significantly decreased. . . ." "The study provides evidence that bacteria from the human colon can hydrogenate C18 essential polyunsaturated fatty acids."

F.A. Howard & C. Henderson, 1999

Because of the way in which the decision to call vitamin E a simple antioxidant was conditioned by the historical setting, there has been a reluctance, until recently, to give much weight to the pathogenicity of

lipid peroxidation and free radicals, partly because lipid peroxidation is only a minor part of the toxicity of the polyunsaturated oils, and there was little support for the investigation of the real nature of their toxicity. This environment has even distorted the actual antioxidant value of the various forms of vitamin E. (For example, see Chen, et al., 2002.)

The people who say that vitamin E is nothing but an antioxidant sometimes take other antioxidants, with, or instead of, vitamin E. BHT, BHA, and many natural compounds (derived from industrial and agricultural wastes) are often said to be "better than vitamin E" as antioxidants. Anything that can be oxidized and reduced (melatonin, estrogen, tryptophan, carotene, etc.) will function as an antioxidant in some system, but in other circumstances, it can be a pro-oxidant.

The people who think there is benefit in the abstract "antioxidant" function seem to be thinking in terms of something that will, like a ubiquitous fire department, put out every little fire as soon as it starts. I think it's more appropriate to think of the biological antioxidant systems as programs for controlling the arsonists before they can set the fires.

Since the requirement for vitamin E decreases as the consumption of unsaturated fats decreases, the requirement, if any, would be very small if we didn't eat significant quantities of those fats.

In the years since the tocopherols were identified as vitamin E, the material sold for research and for use as a nutritional supplement has changed drastically several times, even when it has been given a specific chemical identity, such as mixed tocopherols or d-alpha tocopherol. Variations in viscosity and color, caused by changes in the impurities, have undoubtedly influenced its biological effects, but the ideology about its antioxidant value has kept researchers from finding out what a particular batch of it really is and what it really does.

"We compared the effect of a mixed tocopherol preparation with that of alpha-tocopherol alone on superoxide dismutase (SOD) activity and iNOS expression in cultured myocytes exposed to H-R." "Both tocopherol preparations attenuated cell injury. . . ." "However, mixed-tocopherol preparation was much superior to alpha-tocopherol in terms of myocyte protection. . . ." "Lack of efficacy of commercial tocopherol preparations in clinical trials may reflect absence of gamma- and delta-tocopherols."

Chen *H, Li D, Saldeen T, Romeo F, Mehta JL,Biochem Biophys Res Commun 2002 "Mixed tocopherol preparation is superior to alpha-tocopherol alone against hypoxia-reoxygenation injury.*"

Keeping our diet as free as possible of the polyunsaturated fats, to create something like the "deficiency" state that is so protective (against cancer, trauma, poison, shock, inflammation, infection, etc.) in the animal experiments, seems preferable to trying to saturate ourselves with antioxidants, considering the imperfectly defined nature of the vitamin E products, and the known toxicity of many of the other antioxidants on the market.

The carcinogenic properties of the polyunsaturated fats have been known for more than 50 years, as has the principle of extending the life span by restricted feeding. More recently several studies have demonstrated that the long lived species contain fewer highly unsaturated fats than the short lived species. **Restriction of calories prevents the lipids in the brain, heart, and liver from becoming more unsaturated with aging.** (Lee, et al., 1999; Laganiere, et al., 1993; Tacconi, et al., 1991; R. Patzelt-Wenczler, 1981.)

When cells are grown in tissue culture without the “essential fatty acids,” they become “deficient,” and in that state are very resistant to chemical injury, and can be grown indefinitely. Besides being a simple demonstration of the way in which the polyunsaturated fats sensitize cells to injury (Wey, et al., 1993), these experiments must be an embarrassment to the people who base their argument for the oils’ essentiality on a supposed requirement for “making cell membranes.” Since the cells can multiply nicely in their deficient state, we have to conclude that the oils aren’t needed for “membranes,” or maybe that cells resist injury better “without membranes.”

In the opposite direction, an excess of insulin or prolactin, or a

deficiency of vitamin E, increases the activity of the enzymes that convert linoleic acid into the more highly unsaturated fatty acids. Excess insulin and prolactin are crucially involved in many degenerative diseases.

The highly unsaturated fats suppress respiration in many ways, and these trends toward increased unsaturation with aging, endocrine stress, and vitamin E deficiency parallel the life-long trend toward lower energy production from respiration. Many studies show that vitamin E can protect and improve mitochondrial energy production. (Kikuchi, et al., 1991; Donchenko, et al., 1990, 1983; Guarnieri, et al., 1981, 1982.) But the state of so-called essential fatty acid deficiency not only makes mitochondria very resistant to injury, it greatly intensifies their energy production. Vitamin E supplementation is seldom as effective as the absence of the toxic oils.

Many nutrition charts no longer list liver as a good source of vitamin E, but a large portion of an animal's vitamin E is in its liver. This bias in the dietetic literature can be traced to various sources, but a major influence was the campaign in the 1970s by the drug companies that had patented new forms of synthetic "vitamin A." They had physicians and professors fabricate stories about the great toxicity of natural vitamin A, and placed the stories in national magazines, to clear the field for their supposedly non-toxic products, which have turned out to be disastrously toxic. The result is that many people have fearfully stopped eating liver, because of its vitamin A. The other vitamins in liver, including vitamin K, function very closely with vitamin E, and the stably stored forms of vitamin E are likely to be a good approximation for our needs.

There is still a strong division between what people can say in their professional publications, and what they believe. A man who was influential in designating vitamin E as an antioxidant, M.K. Horwitt, complained when the government raised its recommended vitamin E intake by 50%, because it wasn't supported by new data, and because millions of people get only ten milligrams per day and "are healthy." But he has been taking 200 mg daily (plus aspirin) for many years. He apparently doesn't have very much confidence in the ideas he advocates publicly.

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Gerontology 1993;39(1):7-18. **Modulation of membrane phospholipid fatty acid composition by age and food restriction.** Laganiere S, Yu BP. H.M. "Phospholipids from liver mitochondrial and microsomal membrane preparations were analyzed to further assess the effects of age and lifelong calorie restriction on membrane lipid composition." **"The data revealed characteristic patterns of age-related changes in ad libitum (AL) fed rats: membrane levels of long-chain polyunsaturated fatty acids, 22:4 and 22:5, increased progressively, while membrane linoleic acid (18:2) decreased steadily with age. Levels of 18:2 fell by approximately 40%, and 22:5 content almost doubled making the peroxidizability index**

increase with age." "**We concluded that the membrane-stabilizing action of long-term calorie restriction relates to the selective modification of membrane long-chain polyunsaturated fatty acids during aging.**"

Free Radic Biol Med 1999 Feb;26(3-4):260-5. **Modulation of cardiac mitochondrial membrane fluidity by age and calorie intake.** Lee J, Yu BP, Herlihy JT. **"The fatty acid composition of the mitochondrial membranes of the two ad lib fed groups differed: the long-chain polyunsaturated 22:4 fatty acid was higher in the older group, although linoleic acid (18:2) was lower. DR eliminated the differences."** "Considered together, these results suggest that DR **maintains the integrity of the cardiac mitochondrial membrane fluidity by minimizing membrane damage through modulation of membrane fatty acid profile."**

Lipids 2001 Jun;36(6):589-93. **Effect of dietary restriction on age-related increase of liver susceptibility to peroxidation in rats.** Leon TI, Lim BO, Yu BP, Lim Y, Jeon EJ, Park DK.

Jpn J Pharmacol 1979 Apr;29(2):179-86. **Effect of linoleic acid hydroperoxide on liver microsomal enzymes in vitro.** Masuda Y, Murano T. "Rat liver microsomes incubated with linoleic acid hydroperoxide (LAHPO) lost cytochrome P-450 specifically among the enzymes of microsomal electron transport systems. The loss of cytochrome P-450 content and glucose-6-phosphatase activity by LAHPO was accompanied by an increase in malondialdehyde (MDA) production." "These results suggest the possibility that the loss of microsomal enzyme activities during lipid peroxidation may be attributed **largely to a direct attack on enzyme proteins by lipid peroxides rather than** indirectly to a structural damage of microsomal membranes resulting from peroxidative breakdown of membrane lipids."

Ukr Biokhim Zh 2001 Jan-Feb;73(1):43-7. **[Effect of alpha-tocopherol, tocopheryl quinone and other complexes with tocopherol-binding proteins on the activity of enzymes metabolizing arachidonic acid]** Parkhomets' VP, Silonov SB, Donchenko HV. Palladin Institute of Biochemistry, National Academy of Science of Ukraine, Kyiv. alpha-Tocopherol, tocopherylquinon jointly with the proteins tocopherol acceptors from cytosole **were identified to inhibit the activity of 5-lipoxigenase and so the synthesis of leukotriene A4 at the early stages providing for A4 hydrolase activation and C4 synthesase,** as well as accelerate leukotrienes B4 and C4 synthesis at the further stages respectively changing the final spectrum of leukotriens in the organism tissues. Firstly, the leading role of proteins complexes capable to strengthen the effect of alpha-tocopherol and tocopherylquinon on arachidonic acid oxidative metabolism was determined.

Int J Vitam Nutr Res 1981;51(1):26-33. **[Effect of vitamin E on the synthesis of polyunsaturated fatty acids]** Patzelt-Wenczler R. The formation of polyunsaturated fatty acids is influenced by vitamin E. The enzyme of the endoplasmic reticulum isolated from rat liver responsible for chain elongation and desaturation showed higher activity under vitamin E-deficiency. The activity was raised both per mg protein and per mg DNA. The application of alpha-Tocopherol to the vitamin E-deficient animals caused the normalization of the enzyme activity within 48 hours. This indicates a regulatory function of alpha-Tocopherol in the process of oxidation.

Lipids 2001 May;36(5):491-8. **Correlation of fatty acid unsaturation of the major liver mitochondrial phospholipid classes in mammals to their maximum life span potential.** Portero-Otin M, Bellmunt MJ, Ruiz MC, Barja G, Pamplona R.

Free Radic Biol Med 1999 Oct;27(7-8):729-37. **Age-dependent increase of collagenase expression can be reduced by alpha-tocopherol via protein kinase C inhibition.** Ricciarelli R, Maroni P, Ozer N, Zingg JM, Azzi A. "Our in vitro experiments with skin fibroblasts suggest that alpha-tocopherol may protect against skin aging by decreasing the level of collagenase expression, which is induced by environmental insults and by aging."

Prostaglandins Leukot Essent Fatty Acids 1991 Oct;44(2):89-92. **Inhibition of PGE2 production in macrophages from vitamin E-**

treated rats. Sakamoto W, Fujie K, Nishihira J, Mino M, Morita I, Murota S.

Int J Vitam Nutr Res 1990;60(1):26-34. **The influence of vitamin E on rheological parameters in high altitude mountaineers.** Simon-Schnass I, Korniszewski L. **"The erythrocyte filterability was unaltered in the vitamin E group in comparison with baseline but was significantly impaired in the control group."**

Neurobiol Aging 1991 Jan-Feb;12(1):55-9. **Aging and food restriction: effect on lipids of cerebral cortex.** Tacconi MT, Lligona L, Salmona M, Pitsikas N, Algeri S. In experimental animals dietary restriction reduces the body weight increase due to aging, increases longevity and delays the onset of age-related physiological deterioration, including age-related changes in serum lipids. Little is known about the influence of food restriction on brain lipids, whose concentration and composition have been shown to change with age. We studied whether some biochemical and biophysical parameters of rat brain membranes, known to be modified with age, were affected by a diet low in calories, in which 50% of lipids and 35% of carbohydrates have been replaced by fibers. The diet was started at weaning and maintained throughout the animal's entire life span. Animals fed the low calorie diet survived longer and gained less body weight than standard diet fed rats. Age-related increases in microviscosity, cholesterol/phospholipid and sphingomyelin/phosphatidylcholine ratios were **reduced or restored to the levels of young animals in cortex membranes of 32 old rats fed the low calorie diet, while the age-related increase in mono- to polyunsaturated fatty acid ratios in phospholipids was further raised.** In conclusion we have shown that a diet low in calories and high in fibers affects lipid composition in the rat brain, **in a direction opposite to that normally believed to reduce age-related deterioration of brain functions**.

Toxicol Appl Pharmacol 1993 May;120(1):72-9. **Essential fatty acid deficiency in cultured human keratinocytes attenuates toxicity due to lipid peroxidation.** Wey HE, Pyron L, **Human keratinocytes are commonly grown in culture with a serum-free medium. Under these conditions, keratinocytes become essential fatty acid deficient (EFAD), as determined by gas chromatographic analysis of cell phospholipid fatty acid composition. Exposure of EFAD keratinocytes for 2 hr to concentrations of t-butyl hydroperoxide (tBHP) up to 2 mM did not result in toxicity assessed by lactate dehydrogenase (LDH) release and only a small indication of lipid peroxidation assessed by the release of thiobarbituric acid-reactive substances** (TBARS). Addition of 10 microM linoleic acid (LA) to serum-free medium alleviated the EFAD condition by increasing the phospholipid content of LA and its elongation and desaturation products, arachidonic acid and docosatetraenoic acid. Exposure of LA-supplemented keratinocytes to tBHP resulted in significant LDH (at 1 and 2 mM tBHP) and TBARS (tBHP concentration dependent) release. TBARS release was also significantly elevated in unexposed LA-supplemented keratinocytes (basal release). Co-supplementation with the antioxidant, **alpha-tocopherol succinate (TS) prevented tBHP (1 mM)-induced LDH release in LA-supplemented cultures. TS supplementation also attenuated the effect of tBHP on TBARS release, but when compared to TS-supplemented EFAD cultures, LA** supplementation still led to increased tBHP-induced TBARS release. Keratinocyte cultures are potentially useful as an alternative to animals in toxicology research and testing. It is important, however, that the cell model provide a response to toxic insult similar to that experienced in vivo. Our results suggest that fatty acid and antioxidant nutrition of cultured keratinocytes are important parameters in mediating the toxic effects of lipid peroxidation.

Cancer Lett 1997 Jan 1;111(1-2):179-85. **Subcutaneous, omentum and tumor fatty acid composition, and serum insulin status in patients with benign or cancerous ovarian or endometrial tumors. Do tumors preferentially utilize polyunsaturated fatty acids?** Yam D, Ben-Hur H, Dgani R, Fink A, Shani A, Berry EM.

AC Chan, J. of Nutrition, 1998

"The response-to-injury hypothesis explains atherosclerosis as a chronic inflammatory response to injury of the endothelium, which leads to complex cellular and molecular interactions among cells derived from the endothelium, smooth muscle and several blood

cell components. Inflammatory and other stimuli trigger an overproduction of free radicals, which promote peroxidation of lipids in LDL trapped in the subendothelial space. Products of LDL oxidation are bioactive, and they induce endothelial expression and secretion of cytokines, growth factors and several cell surface adhesion molecules. The last-mentioned are capable of recruiting circulating monocytes and T lymphocytes into the intima where monocytes are differentiated into macrophages, the precursor of foam cells. In response to the growth factors and cytokines, smooth muscle cells proliferate in the intima, resulting in the narrowing of the lumen. Oxidized LDL can also inhibit endothelial production of prostacyclin and nitric oxide, two potent autacoids that are vasodilators and inhibitors of platelet aggregation. Evidence is presented that vitamin E is protective against the development of atherosclerosis. Vitamin E enrichment has been shown to retard LDL oxidation, inhibit the proliferation of smooth muscle cells, inhibit platelet adhesion and aggregation, inhibit the expression and function of adhesion molecules, attenuate the synthesis of leukotrienes and potentiate the release of prostacyclin through up-regulating the expression of cytosolic phospholipase A2 and cyclooxygenase. Collectively, these biological functions of vitamin E may account for its protection against the development of atherosclerosis."

6: Early Hum Dev 1994 Nov 18;39(3):177-88
Vitamin A and related essential nutrients in cord blood: relationships with anthropometric measurements at birth. Ghebremeskel K, Burns L, Burden TJ, Harbige L, Costeloe K, Powell JJ, Crawford M. Institute of Brain Chemistry and Human Nutrition, Queen Elizabeth Hospital for Children, London, UK. Following the advice given by the Department of Health to women who are, or may become pregnant, not to eat liver and liver products because of the risk of vitamin A toxicity, the concentrations of vitamins A and E, and copper, magnesium and zinc in cord blood were investigated. The study was conducted in Hackney, an inner city area of London. Esters of vitamin A were not detected in any of the samples, indicating that there was no biochemical evidence of a risk of toxicity. Indeed, vitamin A correlated significantly with birthweight, head circumference, length, and gestation period. There was also a significant positive relationship between zinc and birthweight. In contrast, copper showed a negative correlation with birthweight and head circumference. Vitamin E and magnesium were not associated with any of the anthropometric measurements, although magnesium showed an increasing trend with birthweight. The data suggest that most of the mothers of the subjects studied may have been marginal with respect to vitamins A and E and zinc. In those with low birthweight babies. a higher intake would have improved their nutritional status and possibly the outcome of their pregnancy. For these low-income mothers, liver and liver products are the cheapest and the best source of vitamins A and E, haem iron, B vitamins and several other essential nutrients; hence the advice of the Department of Health may have been misplaced.

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