Suitable Fats, Unsuitable Fats: Issues in Nutrition

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For fifty years, the mass media have been making the public think about the fats in their diet, filling the culture with clichés about bad saturated animal fats that raise cholesterol, or lately the trans-fats in margarine, and images of arteries clogged by bad fats. The public instruction about the fats we should eat resembles the owner's manual for a car, that tells you what kind of motor oil and fuel and coolant to use; they are telling us that they know how our body works, and that they know what it needs. But now, even after the human genome has supposedly been partly "decoded," the biological functions of the fats have hardly begun to be investigated.

To understand the present issues regarding fats in nutrition and medicine it's helpful to look at the historical development of biochemical and physiological fat research in a variety of contexts, including agriculture and economics, as well as considering the effects of the changing ideas about cell structure, vitamins, hormones, immunology, brain development, evolution, and the growing understanding of the way physiology interacts with ecology. We need to recognize the complexity of the physiology of fats, to appreciate the complexity of the living organism.

Financial considerations have driven fat research in very obvious ways. In 1883, Mark Twain described how commercial fraud was making use of new technology to substitute cheap fats and oils for butter and olive oil.. Hard fats such as tallow, which had been used for making soap and candles, began to be widely used as a substitute for butter in the 19th century. Around 1912, chemists found economical ways to solidify (for use as a butter substitute) the very cheap liquid oils, such as cottonseed oil, linseed oil, whale oil, and fish oils, which been used mostly as fuels or varnish. The seed oils were so cheap that meat packers quickly became major producers of hydrogenated cottonseed and soy oils, to extend their limited supply of lard or tallow for sale as shortening or margarine.

Between 1912 and 1927 there were several studies that reported that animals could live on a fat-free diet, and that in fact they lived longer, and without the normal mortality from cancer. In the 1940s and 1950s, most textbooks that mentioned the idea that certain fats were essential nutrients described it as a controversial idea. But the oil industries used public relations effectively to sell the medical (heart protective) benefits of a diet containing increased amounts of linoleic and linolenic acids, which they called the essential fatty acids. They began citing a 1929 publication (by G. Burr and M. Burr) that claimed to demonstrate the essentiality of those fatty acids, while ignoring the publications that pointed in different directions.

The cheapness of the seed oils led to their use in animal feeds, to promote growth. By the 1940s, the polyunsaturated oils, including fish oils, were known to cause deterioration of the brain, muscles, and gonads in a variety of animals, and this was found to be caused mainly by their destruction of vitamin E. A little later, the disease called steatitis or yellow fat disease was found to be produced in various animals that were fed too much fish or fish oil.

The reason linseed oil and fish oil were used for making varnishes and paints was that they are "drying oils," reacting with oxygen to polymerize and harden. The physical and chemical propertiess of the oils are fairly well understood, and among the polyunsaturated fatty acids (PUFA) the omega -3 fatty acids react most easily with oxygen. Heat, light, and moisture increase their spontaneous interactions with oxygen, and besides polymerizing, these oils produce a variety of reactive particles, including acrolein, which combine with other substances, such as cellular proteins and DNA, with highly toxic effects. At low temperatures and low oxygen concentrations these oils are not highly reactive. Fats that harden at low temperatures (as saturated fats do) wouldn't be convenient for organisms that live in a cool environment, and so organisms regulate the type of fat they synthesize according to the temperature of their tissues. The fact that certain types of polyunsaturated fatty acids function nicely in fish, worms, and insects, doesn't mean that they are ideal fats for mammals.

The fact that vitamin E prevented or cured some of the major diseases in farm animals caused by excessive PUFA, and that it could retard the development of rancidity in stored oils, led quickly to the persistent belief that lipid peroxidation is the only toxic effect of the vegetable oils. However, the oils were being seen to cause other problems, including accelerated aging and obesity, but those problems weren't of interest to farmers, who wanted to sell plump young animals as cheaply and quickly as possible. Even fresh oils have toxic effects, and the oxidative damage they do is often the consequence of these other toxic actions.

Another cheap food additive, coconut oil, was found to increase feed consumption while slowing weight gain, so it wasn't popular in the meat industry. The highly unsaturated seed oils had the opposite effect, of producing a rapid fattening of the animal, while decreasing feed consumption, so by 1950 corn and soybeans were widely considered to be optimal feeds for maximizing profits in the production of meat animals. It was at this time that the industry found that it could market the liquid oils directly to consumers, as health-promoting foods, without bothering to turn them into solid shortening or margarine. Somehow, few physiologists continued to think about the implications of metabolic slowing, obesity, and the related degenerative diseases.

As vitamin research advanced in the 1940s, Roger Williams' lab at the Clayton Foundation Biochemical Institute, University of Texas at Austin, recognized the "fat deficiency disease" of the Burrs as a deficiency of vitamin B6, and showed that when they produced the condition with a diet similar to the one the Burrs had used, they could cure it by administering vitamin B6. In the early 1930s George Burr had discovered that animals on a fat free diet had an extremely high rate of metabolism, but he didn't investigate the important ramifications of that observation, such as their increased need for vitamins and minerals, in accordance with their rate of metabolism. The PUFA slowed metabolism, and that effect was good for agriculture.

The commercial pressure on fat research has created a new way of writing research reports, that several decades earlier wouldn't have been acceptable. For example, the effects of a specific fat on a few of the components of a complex process such as clotting are often described in the title, introduction, and conclusion of an article as if they were revealing a way to prevent

heart disease. The effects of unsaturated fats on cells *in vitro* are often the opposite of their effects in living animals, but editors are allowing authors to claim that their *in vitro* results justify dietary or therapeutic use of the fats. Journals of medicine and nutrition are now preferred sites for commercial press releases, composed to superficially resemble scientific reports.

The suppressive effects of unsaturated fats on mitochondrial energy production have been widely investigated, since it is that effect that makes animal fattening with PUFA so economical. Rather than interpreting that as a toxic effect, using the innate structure and function of the mitochondrion as a point of reference from which to evaluate dietary components, the consumption of "good" oils is being used as the reference point from which to evaluate the meaning of metabolism ("efficiency is good," "low oxygen consumption is good"). Building on the idea that the oils are health-promoters which increase metabolic efficiency, the never-viable "rate of aging" theory was resuscitated: The anti-respiratory effect of PUFA is used (illogically) to return to the idea that aging occurs in proportion to the amount of oxygen consumed, because animals which lack the supposedly essential nutrients ("defective animals") consume oxygen rapidly--burning calories rapidly, they are supposed to be like a candle that won't last as long if it burns intensely. The old theory is simply resuscitated to explain why the anti-respiratory action of PUFA might be beneficial, justifying further promotion of their use as food and drugs.

Ordinarily, in biochemistry and physiology the inhibition of an enzyme is taken as a suggestion of toxicity, but when the point of reference is the idea of the goodness of PUFA, the *activity* of an intrinsic enzyme is taken to be evidence of harm, and its *inhibition* (by PUFA) is taken to be the proper, healthful situation. The enzyme that produces the Mead fatty acid is strongly inhibited by PUFA seed oils (less strongly by fish oils), and so the presence of the Mead acid in the tissues is taken as evidence that the animal is suffering damage resulting from the absence of PUFA. The Mead acid happens to have some valuable anti-inflammatory effects, and is associated with many biological advantages, but research in that direction is prevented by the lack of funding.

By 1920, the polyunsaturated fatty acids were recognized to inhibit proteolytic enzymes. At that time, the production of unsaturated fat was considered to be a feature of certain pathogens, able to overcome the proteolytic-phagocytic functions of the immune system.

Scattered studies have found that polyunsaturated fats inhibit the proteolytic enzymes involved in the digestion of food, in the removal of clots, in the formation of thyroid hormone, and many other essential physiological processes. But currently, the only implication being drawn from this broad class of effects of the PUFA is that some proteolytic enzymes are involved in disease processes, and consequently increased consumption of PUFA would be appropriate, because of their ability to suppress a conditionally harmful proteolytic enzyme. Since the organism consists mainly of proteins, there are complex innate systems for regulating the proteolytic enzymes, activating or inactivating them as needed, and such complexity isn't likely to depend on variable, unstable dietary factors. Exogenous substances that inhibit some proteases could create an unlimited variety of functional and anatomical irregularities.

Some of the interesting enzymes affected specifically by polyunsaturated fatty acids are those involved in hormone production. While they inhibit the formation of progesterone and androgens, they activate the synthesis of estrogen, which in turn activates the release of more free polyunsaturated fatty acids from the tissues, in a positive feedback pattern.

The inhibition of detoxification enzymes by PUFA (Tsoutsikos, et al., 2004) affects many processes, such as the elimination of estrogen, contributing to the positive feedback between estrogen and the oils. The meaning of this tends to be lost, because of the estrogen industry's effective campaigns.

Another situation in which fatty acids participate in a positive feedback system is the stress reaction, in which the released fatty acids impair mitochondrial energy production, increasing the stress and leading to further release of fatty acids.

One of the perennial theories of aging that has remained viable is the metaplasm/lipofuscin/age pigment theory, the idea that a toxic material accumulates in tissues over time. The age pigment contains proteins, cross-linked PUFA, and metals. The inhibition of proteolytic enzymes is involved in its accumulation, and the ratio of PUFA to saturated fatty acids is an important factor in its formation. Estrogen is one of the factors that can promote the formation of age pigment, probably partly because its lipolytic action increases the cells' exposure to free fatty acids. The lipofuscin contributes to inhibition of proteolysis, probably partly through increased production of free radicals and hydrogen peroxide.

The proteolytic enzymes are an essential part of innate immunity, and the highly unsaturated fatty acid, EPA, which is the most immunosuppressive of the fats, strongly inhibits proteolysis in some cells. The natural killer (NK) cells and phagocytic cells are two types of cell that are suppressed by PUFA, and they are involved in many kinds of physiological events, not just the killing of tumor cells and virus infected cells.

The immunosuppressive effects of PUFA are very general. Many metabolites that are known to have harmful effects on the immune system are increased by the PUFA (histamine [Masini, et al., 1990], serotonin, lactate, nitric oxide [Omura, et al., 2001]). These substances are also involved in tumor development.

Besides inhibiting enzymes and being converted into prostaglandins, the polyunsaturated fatty acids have direct effects, as signals (or interference with signals) on many tissues. The belief that the PUFA are essential nutrients has influenced the way cellular excitability thresholds are being interpreted. Anxiety and panic may be interpreted as alertness, calmness may be interpreted as stupidity. Specifically, long-term potentiation (LTP) may contribute to seizures, senility, and excitotoxicity, as well as to learning, but many titles and conclusions equate increased LTP with "improved LTP," implying that it has biological value to the animal.

The ability of nerve cells to become quiescent after excitation is essential to learning and perception. This ability is lost with aging, as the functional balance in the brain shifts away from GABA-ergic to glutamatergic nerves. The polyunsaturated fatty acids promote the excitatory nervous state. The combination of respiratory inhibition with excitation can produce excitotoxic

cell death. If the doctrine of "essentiality of PUFA" hadn't been so influential, different interpretations of excitatory thresholds, energy metabolism, and even cell structure would have been allowed to develop more fully.

The concentration of polyunsaturated fats in the brain has led many people to say that the "nutritionally essential fatty acids," especially the omega -3 fatty acids, are essential for brain development (for the formation of nerve cell membranes), and for the formation of synapses, and that increasing the amount of those fats in the diet would be desirable. The types of argument they use simply ignore the real evidence**:** Cells can multiply indefinitely in culture dishes without the essential fatty acids, insects can multiply for generations on diets without the unsaturated fats, forming normal synapses and brains, and mammals fed diets with extremely small amounts of the unsaturated fats grow with perfectly normal--possibly superior--brains.

One of the fats in the omega -9 series, that the human body can synthesize, nervonic acid, is a major constituent of brain tissue, but its important functions in brain development have hardly been investigated. Unlike the unsaturated fatty acids oleic acid, linoleic acid, and eicosapentaenoic acid (EPA), nervonic acid isn't associated with the "coronary risk factors," and it has been suggested that it might be used in adults to prevent obesity-related diseases. (Oda, et al., 2005).

One major area of research that has been neglected involves the role of fats in modifying the ways in which proteins and nucleic acids interact with water--arguably the most basic of all physiological processes. Unsaturated fats are more water soluble than saturated fats, and they are involved in many problems of permeability and edema.

In aging and evolution, there are systematic changes in tissue water content that appear to correspond to changes in rate of metabolism, to the degree of unsaturation of cellular fats, and to thyroid function and temperature. Metabolic intensity and longevity can be modified by changing the degree of saturation of fats in the diet and tissues, but--despite almost a century of sporadic investigations--no one has yet worked out in detail the most appropriate way to do this. But it has become clear that the "uncoupled" mitochondrion, that "wastes oxygen and calories," is protective against free radicals, cancer, and aging. Thyroid hormone and the absence of PUFA are important factors in supporting the "wasteful" mitochondrion.

Although the complex interactions of anatomy, energy, temperature, fat nutrition, tissue water content, and hormones haven't been systematically investigated, some of the principles regarding the biological suitability of specific fats are already being applied in the limited context of therapy.

At present, the most important issue is to recognize the dangers presented by the intrusion of corporate power into science, especially as it relates to nutrition and medicine, and to consider the implications of the known effects of the PUFA on all of our biological systems.

The food-derived polyunsaturated fatty acids play important roles in the development of all of the problems associated with aging--reduced immunity, insomnia, decreased learning ability, substitution of fat for muscle, susceptibility to tissue peroxidation and inflammation, growth of tumors, etc., and are probably involved in most other health problems, even in children. If research hadn't been guided by the economic interests of the seed oil industry, many of those problems would have been solved by now.

The influence of the mass media on science can be seen in two issues that are currently well known.

A popular test used for evaluating diabetes is the measurement of glycated hemoglobin, the attachment of a sugar-like fragment to the protein of hemoglobin. This is used to judge whether blood sugar is being controlled adequately. The glycation of proteins is widely believed to be a central process in aging, and is often used to argue that people should reduce their sugar consumption.

Another well publicized problem supposedly involving the reaction between sugars and proteins has to do with the discovery of the carcinogen, acrylamide, in breads and french fries. The Whole Foods Market was sued in California for selling whole wheat bread without a warning that it contained a carcinogen.

But the changes in proteins that occur in diabetes are mainly produced by the breakdown products of polyunsaturated fatty acids. Acrylamide is produced largely by the reaction of PUFA with proteins.

Sugar, by reducing the level of free fatty acids in the body, actually tends to protect against these toxic effects of the PUFA. Diabetes, like cancer, has been known for a long time to be promoted by unsaturated oils in the diet, rather than by sugar. The seed oil industry has been more effective than the sugar industry in lobbying and advertising, and the effects can be seen in the assumptions that shape medical and biological research.

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starting two weeks before the initiation. An increase in the n-3/n-6 ratio did not suppress the incidence or reduce the latency of mammary tumor development. The number and weight of mammary tumors per tumor-bearing rat tended to be large in the group with an n-3/n-6 ratio of 7.84 compared with those in the other groups. **As the n-3/n-6 ratios were elevated, the total number and weight of tumors increased gradually."** "These results suggested that the increase in the n-3/n-6 ratio of dietary fat with the fixed PUFA-to-saturated fatty acid ratio cannot suppress the mammary carcinogenesis but can promote development of tumors, despite reduced PGE2 concentration in the tumor."

J Cardiovasc Pharmacol. 2006 Mar;47(3):493-9. **Mildronate, a novel fatty acid oxidation inhibitor and antianginal agent, reduces myocardial infarct size without affecting hemodynamics.** Sesti C, Simkhovich BZ, Kalvinsh I, Kloner RA. "Mildronate is a fatty acid oxidation inhibitor approved as an antianginal drug in parts of Europe."

J Nutr 2000 Dec;130(12):3028-33. **Polyunsaturated (n-3) fatty acids susceptible to peroxidation are increased in plasma and tissue lipids of rats fed docosahexaenoic acid-containing oils.** Song JH, Fujimoto K, Miyazawa T.. "Thus, high incorporation of (n-3) fatty acids (mainly DHA) into plasma and tissue lipids due to DHA-containing oil ingestion may undesirably affect tissues by enhancing susceptibility of membranes to lipid peroxidation and by disrupting the antioxidant system."

Diabetes Nutr Metab. 2002 Aug;15(4):205-14. **Long-term effect of fish oil diet on basal and stimulated plasma glucose and insulin levels in ob/ob mice.** Steerenberg PA, Beekhof PK, Feskens EJ, Lips CJ, Hoppener JW, Beems RB. "We have investigated, in comparison to low and high fat diets, the effect of a fish oil diet on basal and stimulated plasma glucose and insulin levels in male and female ob/ob mice." "Intercurrent deaths were found especially in the fish oil diet group. Compared to the other diet groups, plasma insulin levels of the fish oil diet group were significantly increased 3 months after the start of the diet and remained higher for another 3 months." "At 12 months, microscopy revealed an increased severity of hepatic brown pigment accumulation and extramedullary haematopoiesis in the spleen of mice fed with fish oil." "Fish oil diet also increased intercurrent mortality. However, a consistent course of death could not be established using morphological parameters."

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J Biol Chem. 2005 Oct 28;280(43):35896-903. Epub 2005 Aug 23. **Unsaturated fatty acids phosphorylate and destabilize ABCA1 through a phospholipase D2 pathway.** Wang Y, Oram JF. "ATP-binding cassette transporter ABCA1 mediates the transport of cholesterol and phospholipids from cells to HDL apolipoproteins and thus modulates HDL levels and atherogenesis. Unsaturated fatty acids, which are elevated in diabetes, impair the ABCA1 pathway in cultured cells by destabilizing ABCA1 protein." "Unsaturated but not saturated fatty acids stimulated phospholipase D (PLD) activity, the PLD inhibitor 1-butanol prevented the unsaturated fatty acid-induced reduction in ABCA1 levels, and the PLD2 activator mastoparan markedly reduced ABCA1 protein levels, implicating a role for PLD2 in the ABCA1 destabilizing effects of fatty acids." "These data provide evidence that intracellular unsaturated acyl-CoA derivatives destabilize ABCA1 by activating a PLD2 signaling pathway."

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