Fats, functions & malfunctions

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Saturated fatty acids terminate the stress reactions, polyunsaturated fatty acids amplify them.

The most highly unsaturated fats, including DHA, accumulate with aging, and their toxic fragments are increased in Alzheimer's disease.

The most highly unsaturated fats found in fish oil break down into chemicals that block the use of glucose and oxygen.

The ratio of saturated fatty acids to polyunsaturated fatty acids is decreased in cancer. Omega-3 fats promote metastasis.

Around the beginning of the 20th century, it was commonly believed that aging resulted from the accumulation of insoluble metabolic by-products, sort of like the clinker ash in a coal furnace. Later, age pigment or lipofuscin, was proposed to be such a material. It is a brown pigment that generally increases with age, and its formation is increased by consumption of unsaturated fats, by vitamin E deficiency, by stress, and by exposure to excess estrogen. Although the pigment can contribute to the degenerative processes, aging involves much more than the accumulation of insoluble debris; aging increases the tendency to form the debris, as well as vice versa.

There is a growing recognition that a persistent increase of free fatty acids in the serum, which is seen in shock, heart failure, and aging, indicates a bad prognosis, but there is no generally recognized explanation for the fact that free fatty acids are harmful. I want to mention some evidence showing that it is the accumulation of polyunsaturated fats in the body that makes them harmful.

The physical and functional properties of saturated fatty acids and polyunsaturated fatty acids (PUFA) are as different from each other as day is from night. The different fatty acids are directly involved, very often with opposite effects, in cell division and growth, cell stability and dissolution, the organization of cells, tissues, and organs, the regulation of pituitary hormones, adrenalin and sympathetic nervous activation, histamine and serotonin synthesis, adrenal cortex hormones, thyroid hormones, testosterone, estrogen, activators of the immune system and inflammation (cytokines), autoimmune diseases, detoxification, obesity, diabetes, puberty, epilepsy,

Parkinson's disease, other degenerative nerve diseases and Alzheimer's disease, cancer, heart failure, atherosclerosis, and strokes. In each of these situations, the PUFA have harmful effects.

Most people are surprised to hear about the systematically harmful effects of the common dietary polyunsaturated fats and the protective effects of saturated fats. That's because there is a pervasive mythology of fats in our culture. Officials are proposing to tax saturated fats. Laws are being passed prescribing the fats that can be served in restaurants, and people write letters to editors about them, and great amounts of money are spent publicizing the importance of eating the right fats. Their focus is on obesity, atherosclerosis, and heart disease. The details of the myth change a little, as new fat products and industries appear.

As I understand the basic myth, the difference between the "essential" polyunsaturated fats and the saturated fats has to do with their shape---the unsaturated fatty acids bend or fold in a way that makes them more mobile than saturated fats of the same length, and this causes the all-important "membranes" of cells to be more fluid, and thus to have "better functions," though the myth isn't very clear on the issue of fluidity and functionality. At that point, it passes responsibility to the more fundamental biological myth, of the metabolically active cell membrane.

Practically everyone learns, in grade school and from television, about the good and the bad oils, and cell membranes, but it might seem likely that people who spend their lives investigating the role of fats in organisms would have acquired a different, more complicated, view. But one of the most famous food fat researchers, J.M. Bourre, has succinctly (and thoughtlessly) expressed his understanding of the function of fatty substances in the body: "In fact the brain, after adipose tissue, is the organ richest in lipids, whose only role is to participate in membrane structure." (J.M. Bourre, 2004.) The fact that his editor let him publish the statement shows how the myth functions, causing people to accept things because they are "common knowledge." The influence of the medical and pharmaceutical industries is so pervasive that it becomes the context for most biological research.

Luckily, many people are working outside the myth, in specialized problems of physiology and cell biology, and their observations are showing a reality much more complex and interesting than the mythology.

When we eat more protein or carbohydrate than we need, the excess can be converted to fats, to be stored (as triglycerides), but even on a maintenance diet we synthesize some fats that are essential parts of all of our cells, including a great variety of phospholipids. People seldom talk about the importance of fats in the nucleus of the cell, but every nucleus contains a variety of lipids--phospholipids, sphingolipids, cholesterol, even triglycerides--similar to those that are found elsewhere in the cell and in every part of the body, including the brain (Balint and Holczinger, 1978; Irvine, 2002). Phospholipids are often considered to be "membrane lipids," but they have been demonstrated in association with elements of the cell's skeleton, involved in cell division, rather than in membranes (Shogomori, et al., 1993).

The cytoskeleton, a fibrous framework of the cell that's responsible for maintaining the organized structure of the cell, internal movement of organelles, coordination, locomotion, and cell division, is made up of three main kinds of protein, and all

of these are affected differently by different kinds of fat.

Actions of lipids on the cell skeleton can change cells' movements, migrations, and invasiveness. Unsaturated fats cause clumping of some types of cell filament, condensation and polymerization of other types, in ways that are associated with brain degenerative diseases and cancer. For example, DHA alters the structure of the protein alpha-synuclein, causing it to take the form seen in Parkinson's disease and other brain conditions. The synucleins regulate various structural proteins, and are affected by stress, aging, and estrogen exposure, as well as by the polyunsaturated fats. One type of synuclein is involved in the promotion of breast cancer. Saturated fatty acids have exactly the opposite effects of PUFA on the synucleins, reversing the polymerization caused by the PUFA (Sharon, et al., 2003).

When cancers are metastasizing, their phospholipids contain less stearic acid than the less malignant tumors (Bougnoux, et al., 1992), patients with advanced cancer had less stearic acid in their red blood cells (Persad, et al., 1990), and adding stearic acid to their food delayed the development of cancer in mice (Bennett, 1984). The degree of saturation of the body's fatty acids corresponds to resistance to several types of cancer that have been studied (Hawley and Gordon, 1976; Singh, et al., 1995).

The phospholipids are being discussed in relation to drugs that can modify "signaling" by acting on phospholipid receptors, using language that was developed in relation to hormones. A surface barrier membrane, with receptors that send signals to the nucleus, is invoked by many of the recent discussions of phospholipids. There's no question that the fats do affect regulatory processes, but the theory and the language should correspond to the physiological and ecological realities. Vernadski's metaphor, that an organism is a "whirlwind of atoms," is probably more appropriate than "targeted signals and receptors" for understanding the physiology of fatty acids and phospholipids. The rate of change and renewal of these structural fats is very high. In rats, one study found a 30% decrease in the total phospholipid pool in the brain in the first 30 minutes after death (Adineh, et al., 2004). Another study in the brains of living rats found that a particular class of brain lipids, ethanolamine plasmalogens, had a turnover time of about 5 hours (Masuzawa, et al., 1984). (This type of lipid is an important component of the lipoproteins secreted by the liver into the serum [Vance, 1990], and is also a major lipid in the heart and brain.) Stresses such as the loss of sleep cause great distortions in phospholipid metabolism throughout the body, especially in the brain and liver.

Actions of lipids on the cell skeleton can change cells' movements, migrations, and invasiveness, even in short term experiments. The effects of the "essential fatty acid" linoleic acid have been compared to the drug colchicine, which is known to interfere with the cell skeleton and cell division. According to Hoover, et al., (1981), it disturbed the structure of the cytoskeleton more than colchicine does; it caused the cell filaments to clump together, while saturated fatty acids didn't have such an effect.

The fatty molecules that participate in the normal cell functions are made by cells even when they are grown in a fat-free solution in a culture dish. They include saturated fatty acids such as palmitate and stearate, and omega-9 unsaturated fats, such as oleic acid and omega-9 polyunsaturated fatty acids. The saturated fatty acids found in the nucleus associated with the chromosomes are resistant to change when the composition of the animal's diet changes (Awad and Spector, 1976), while the unsaturated fats change according to the diet. These intracellular fats are essential for cell division and the regulation of the genes, and for cell survival (Irvine, 2002). Although cells make the saturated fats that participate in those basic functions, the high rate of metabolism means that some of the lipids will quickly reflect in their structure the free fatty acids that circulate in the blood. The fats in the blood reflect the individual's diet history, but recently eaten fats can appear in the serum as free fatty acids, if the liver isn't able to convert them into triglycerides.

The polyunsaturated fatty acids differ from the saturated fats in many ways, besides their shape and their melting temperature, and each type of fatty acid is unique in its combination of properties. The polyunsaturated fatty acids, made by plants (in the case of fish oils, they are made by algae), are less stable than the saturated fats, and the omega-3 and omega-6 fats derived from them, are very susceptible to breaking down into toxins, especially in warm-blooded animals. Other differences between saturated and polyunsaturated fats are in their effects on surfaces (as surfactant), charges (dielectric effects), acidity, and their solubility in water relative to their solubility in oil. The polyunsaturated fatty acids are many times more water soluble than saturated fatty acids of the same length. This property probably explains why only palmitic acid functions as a surfactant in the lungs, allowing the air sacs to stay open, while unsaturated fats cause lung edema and respiratory failure.

The great difference in water/oil solubility affects the strength of binding between a fatty acid and the lipophilic, oil-like, parts of proteins. When a protein has a region with a high affinity for lipids that contain double bonds, polyunsaturated fatty acids will displace saturated fats, and they can sometimes displace hormones containing multiple double bonds, such as thyroxine and estrogen, from the proteins that have a high specificity for those hormones. Transthyretin (also called prealbumin) is important as a carrier of the thyroid hormone and vitamin A. The unsaturation of vitamin A and of thyroxin allow them to bind firmly with transthyretin and certain other proteins, but the unsaturated fatty acids are able to displace them, with an efficiency that increases with the number of double bonds, from linoleic (with two double bonds) through DHA (with six double bonds).

The large amount of albumin in the blood is important in normal fatty acid binding and transport, but it is also an important part of our detoxifying system, since it can carry absorbed toxins from the intestine, lungs, or skin to the liver, for detoxification. Albumin facilitates the uptake of saturated fatty acids by cells of various types (Paris, et al., 1978), and its ability to bind fatty acids can protect cells to some extent from the unsaturated fatty acids (e.g., Rhoads, et al., 1983). The liver's detoxification system processes some polyunsaturated fats for excretion, along with hormones and environmental toxins.

The movement of proteins from the plasma into cells has often been denied, but there is clear evidence that a variety of proteins, including IgG, transferrin haptoglobin, and albumin can be found in a variety of cells, even in the brain (Liu, et al.,

1989). Cells are lipophilic, and absorb molecules in proportion to their fattiness; this long ago led people to theorize that cells are coated with a fat membrane.

The idea of a semipermeable membrane, similar in function to the membrane inside an egg shell, was proposed about 150 years ago, to explain the ability of living cells to concentrate certain chemicals, such as potassium ions, while excluding others, such as sodium ions. This idea of a molecular sieve was shown to be invalid when radioactive isotopes made it possible to observe that sodium ions diffuse freely into cells, and it was replaced by the idea of a metabolically active membrane, containing "pumps" that made up for the inability to exclude various things, and that allowed cells to retain high concentrations of some dissolved substances that are free to diffuse out of the cell. The general idea of the membrane as a barrier persisted as a sort of "common sense" idea, that has made people ignore experiments that show that some large molecules, including some proteins, can quickly and massively enter cells. Albumin and transthyretin are two proteins that are sometimes found in large quantities inside cells, and their primary importance is that they bind and transport biologically active oily molecules.

While the competition by PUFA for protein binding sites blocks the effects of thyroid hormone and vitamin A, the action of PUFA on the sex steroid binding protein (SBP, or SSBG, for sex steroid binding globulin) increases the activity of estrogen. That's because the SSBG neutralizes estrogen by binding it, keeping it out of cells; free PUFA keep it from binding estrogen (Reed, et al., 1986). People with low SSBG/estrogen ratio have an increased risk of cancer. When the SSBG protein is free of estrogen, it is able to enter cells, and in that estrogen-free state it probably serves a similar protective function, capturing estrogen molecules that enter cells before they can act on other proteins or chromosomes. Transthyretin, the main transporter of thyroid and vitamin A, and albumin (which can also transport thyroid hormone) are both able to enter cells, while loaded with thyroid hormone and vitamin A. Albumin becomes more lipophilic as it binds more lipid molecules, so its tendency to enter cells increases in proportion to its fat burden. Albumin in the urine is a problem associated with diabetes and kidney disease; albumin loaded with fatty acids passes from the blood into the urine more easily than unloaded albumin, and it is the fatty acids, not the albumin, which causes the kidney damage (Kamijo, et al., 2002). It's possible that SSBG's opposite behavior, entering cells only when it carries no hormones, is the result of becoming less lipophilic when it's loaded with estrogen.

Since most people believe that cells are enclosed within a barrier membrane, a new industry has appeared to sell special products to "target" or "deliver" proteins into cells across the barrier. Combining anything with fat makes it more likely to enter cells. Stress (which increases free fatty acids and lowers cell energy) makes cells more permeable, admitting a broader range of substances, including those that are less lipophilic.

Linoleic acid and arachidonic acid, which are said to "make the lipid membrane more permeable," in fact make the whole cell more permeable, by binding to the structural proteins throughout the cell, increasing their affinity for water, causing generalized swelling, as well as mitochondrial swelling (leading to reduced oxidative function or disintegration), allowing more calcium to enter the cell, activating excitatory processes, stimulating a redox shift away from oxidation and toward inflammation, leading to either (inappropriate) growth or death of the cell.

When we don't eat for many hours, our glycogen stores decrease, and adrenaline secretion is increased, liberating more glucose as long as glycogen is available, but also liberating fatty acids from the fatty tissues. When the diet has chronically contained more polyunsaturated fats than can be oxidized immediately or detoxified by the liver, the fat stores will contain a disproportionate amount of them, since fat cells preferentially oxidize saturated fats for their own energy, and the greater water solubility of the PUFA causes them to be preferentially released into the bloodstream during stress.

In good health, especially in children, the stress hormones are produced only in the amount needed, because of negative feedback from the free saturated fatty acids, which inhibit the production of adrenalin and adrenal steroids, and eating protein and carbohydrate will quickly end the stress. But when the fat stores contain mainly PUFA, the free fatty acids in the serum will be mostly linoleic acid and arachidonic acid, and smaller amounts of other unsaturated fatty acids. These PUFA stimulate the stress hormones, ACTH, cortisol, adrenaline, glucagon, and prolactin, which increase lipolysis, producing more fatty acids in a vicious circle. In the relative absence of PUFA, the stress reaction is self limiting, but under the influence of PUFA, the stress response becomes self-amplifying.

When stress is very intense, as in trauma or sepsis, the reaction of liberating fatty acids can become dangerously counter-productive, producing the state of shock. In shock, the liberation of free fatty acids interferes with the use of glucose for energy and causes cells to take up water and calcium (depleting blood volume and reducing circulation) and to leak ATP, enzymes, and other cell contents (Boudreault and Grygorczyk, 2008; Wolfe, et al., 1983; Selzner, et al, 2004; van der Wijk, 2003), in something like a systemic inflammatory state (Fabiano, et al., 2008) often leading to death.

The remarkable resistance of "essential fatty acid deficient" animals to shock (Cook, et al., 1981; Li et al., 1990; Autore, et al., 1994) shows that the polyunsaturated fats are centrally involved in the maladaptive reactions of shock. The cellular changes that occur in shock--calcium retention, leakiness, reduced energy production--are seen in aging and the degenerative diseases; the stress hormones and free fatty acids tend to be chronically higher in old age, and an outstanding feature of old age is the reduced ability to tolerate stress and to recover from injuries.

Despite the instability of polyunsaturated fatty acids, which tend to break down into toxic fragments, and despite their tendency to be preferentially liberated from fat cells during stress, the proportion of them in many tissues increases with age (Laganiere and Yu, 1993, 1987; Lee, et al., 1999; Smidova, et al., 1990;Tamburini, et al., 2004; Nourooz-Zadeh J and Pereira, 1999). This progressive increase with age can be seen already in early childhood (Guerra, et al., 2007). The reason for this increase seems to be that the saturated fatty acids are preferentially oxidized by many types of cell, (fat cells can slowly oxidize fat for their own energy maintenance). Albumin preferentially delivers saturated fatty acids into actively metabolizing cells such at the heart (Paris, 1978) for use as fuel. This preferential oxidation would explain Hans Selye's results, in which canola oil in the diet caused the death of heart cells, but when the animals received stearic acid in addition to the canola oil,

their hearts showed no sign of damage.

Since healthy cells are very lipophilic, saturated fatty acids would have a greater tendency to enter them than the more water soluble polyunsaturated fats, especially those with 4, 5, or 6 double bonds, but as cells become chronically stressed they more easily admit the unsaturated fats, which slow oxidative metabolism and create free radical damage. The free radicals are an effect of stress and aging, as well as a factor in its progression.

When stress signals activate enzymes in fat cells to release free fatty acids from the stored triglycerides, the enzymes in the cytoplasm act on the surface of the droplet of fat. This means that the fatty acids with the greatest water solubility will be liberated from the fat to move into the blood stream, while the more oil soluble fatty acids will remain in the droplet. The long chain of saturated carbon atoms (8 in the case of oleic acid, 15 in palmitic acid, and 17 in stearic acid) in the "tail" of oleic, palmitic, and stearic acid will be buried in the fat droplet, while the tail of the n-3 fatty acids, with only 2 saturated carbons, will be the most exposed to the lipolytic enzymes. This means that the n-3 fatty acids are the first to be liberated during stress, the n-6 fatty acids next. Saturated and monounsaturated fatty acids are selectively retained by fat cells (Speake, et al., 1997).

Women are known to have a greater susceptibility than men to lipolysis, with higher levels of free fatty acids in the serum and liver, because of the effects of estrogen and related hormones.

Women on average have more DHA circulating in the serum than men (Giltay, et al., 2004; McNamara, et al., 2008; Childs, et al., 2008). This highly unsaturated fatty acid is the first to be liberated from the fat stores under stress, and, biologically, the meaning of estrogen is to mimic stress. Estrogen and polyunsaturated fatty acids have similar actions on cells, increasing their water content and calcium uptake. Long before the Women's Health Initiative reported in 2002 that the use of estrogen increased the risk of dementia, it was known that the incidence of Alzhemer's disease was 2 or 3 times higher in women than in men. Men with Alzheimer's disease have higher levels of estrogen than normal men (Geerlings, et al., 2006). The amount of DHA in the brain (and other tissues) increases with aging, and its breakdown products, including neuroprostanes, are associated with dementia. Higher levels of DHA and total PUFA are found in the plasma of demented patients (Laurin, et al., 2003).

Another interesting association of the highly unsaturated fats and estrogen in relation to brain function is that DHA increases the entry of estrogen into the pregnant uterus, but inhibits the entry of progesterone (Benassayag, et al., 1999), which is crucial for brain cell growth. When Dirix, et al., (2009) supplemented pregnant women with PUFA, they found that fetal memory was impaired.

The crucial mitochondrial respiratory enzyme, cytochrome c oxidase, declines with aging (Paradies, et al., 1997), as the lipid cardiolipin declines, and the enzyme's activity can be restored to the level of young animals by adding cardiolipin. The composition of cardiolipin changes with aging, "specifically an increase in highly unsaturated fatty acids" (Lee, et al., 2006). Other lipids, such as a phosphatidylcholine containing two myristic acid groups, can support the enzyme's activity (Hoch, 1992). Even supplementing old animals with hydrogenated peanut oil restores mitochondrial respiration to about 80% of normal (Bronnikov, et al., 2010).

Supplementing thyroid hormone increases mitochondrial cardiolipin (Paradies and Ruggiero, 1988). Eliminating the polyunsaturated fats from the diet increases mitochondrial respiration (Rafael, et al., 1984).

Excitotoxicity is the process in which activation of a nerve cell beyond its capacity to produce energy injures or kills the cell, by increasing intracellular calcium. Glutamic acid and aspartic acid are the normal neurotransmitter excitatory amino acids. Estrogen increases the activity of the excitatory transmitter glutamate (Weiland, 1992), and glutamate increases the release of free fatty acids (Kolko, et al., 1996). DHA (more strongly even than arachidonic acid) inhibits the uptake of the excitotoxic amino acid aspartate, and in some situations glutamate, prolonging their actions. Thymocytes are much more easily killed by stress than nerve cells, and they are easy to study. The PUFA kill them by increasing their intracellular calcium. The toxicity of DHA is greater than that of EPA, whose toxicity is greater than alpha-linolenic acid, and linoleic acid was the most potent (Prasad, et al., 2010). Excitotoxicity is probably an important factor in Alzheimer's disease (Danysz and Parsons, 2003).

When the brain is injured, DHA and arachidonic acid contribute to brain edema, weakening the blood-brain-barrier, increasing protein breakdown, inflammation, and peroxidation, while a similar amount of stearic acid in the same situation caused no harm (Yang, et al., 2007). In other situations, such as the important intestinal barrier, EPA and DHA also greatly increased the permeability (Dombrowsky, et al., 2011).

The process by which excitotoxicity kills a cell is probably a foreshortened version of the aging process.

Excitotoxins (including endotoxin) increase the formation of neuroprostanes and isoprostanes (from n-3 and n-6 PUFA) (Milatovic, et al., 2005), and acrolein and other fragments, which inhibit the use of glucose and oxygen. DHA and EPA produce acrolein and HHE, which react with lysine groups in proteins, and modify nucleic acids, changing the bases in DNA.

Increased intracellular calcium activates lipolysis (by phospholipases), producing more free fatty acids, as well as excitation and protein breakdown, and in the brain neurodegenerative diseases, calcium excess contributes to the clumping of synuclein (Wojda, et al., 2008), an important regulator of the cytoskeletal proteins. The reduced function of normal synuclein makes cells more susceptible to excitotoxicity (Leng and Chuang, 2006).

If the cells adapt to the increased calcium, rather than dying, their sensitivity is reduced. This is probably involved in the "defensive inhibition" seen in many types of cell. In the brain, DHA and arachidonic acid "brought the cells to a new steady state of a moderately elevated [intracellular calcium] level, where the cells became virtually insensitive to external stimuli. This new steady state can be considered as a mechanism of self-protection" (Sergeeva, et al., 2005). In the heart, the PUFAs decreased the sensitivity to stimulation (Coronel et al., 2007) and conduction velocity (Tselentakis, et al., 2006; Dhein, et al.,

2005). Both DHA and EPA inhibit calcium-ATPase (which keeps intracellular calcium low to allow normal neurotransmission) in the cerebral cortex; this suggests "a mechanism that explains the dampening effect of omega-3 fatty acids on neuronal activity" (Kearns and Haag, 2002).

In normal aging, most processes are slowed, including nerve conduction velocity, and conduction velocity in the heart (Dhein and Hammerath, 2001). A similar "dampening" or desensitization is seen in sensory, endocrine, and immune systems, as well as in energy metabolism. Calorie restriction, by decreasing the age-related accumulation of PUFA (20:4, 22:4, and 22:5), can prevent the decrease of sensitivity, for example in lymphoid cells (Laganier and Fernandes, 1991). The known effects of the unsaturated fats on the organizational framework of the cell are consistent with the changes that occur in aging.

One of the essential protective functions that decline with aging is the liver's ability to detoxify chemicals, by combining them with glucuronic acid, making them water soluble so that they can be excreted in the urine. The liver (and also the intestine and stomach) efficiently process DHA by glucuronidation (Little, et al., 2002). Oleic acid, one of the fats that we synthesize ourselves, increases (about 8-fold) the activity of the glucuronidation process (Krcmery and Zakim, 1993; Okamura, et al., 2006). However, this system is inhibited by the PUFA, arachidonic acid (Yamashita, et al., 1997), and also by linoleic acid (Tsoutsikos, et al., 2004), in one of the processes that contribute to the accumulation of PUFA with aging.

Animals that naturally have a relatively low level of the highly unsaturated fats in their tissues have the greatest longevity. For example, the naked mole rate has a life expectancy of more than 28 years, about 9 times as long as other rodents of a similar size. Only about 2% to 6% of its phospholipids contain DHA, while about 27% to 57% of the phospholipids of mice contain DHA Mitchell, et al., 2007).

The famously long-lived people of Azerbaijan eat a diet containing a low ratio of unsaturated to saturated fats, emphasizing fruits, vegetables, and dairy products (Grigorov, et al., 1991).

Some of the clearest evidence of the protective effects of saturated fats has been published by A.A. Nanji's group, showing that they can reverse the inflammation, necrosis, and fibrosis of alcoholic liver disease, even with continued alcohol consumption, while fish oil and other unsaturated fats exacerbate the problem (Nanji, et al., 2001). Glycine protects against fat accumulation in alcohol-induced liver injury (Senthilkumar, et al., 2003), suggesting that dietary gelatin would complement the protective effects of saturated fats.

The least stable n-3 fats which accumulate with age and gradually reduce energy production also have their short term effects on endurance. Endurance was much lower in rats fed a high n-3 fat diet, and the effect persisted even after 6 weeks on a standard diet (Ayre and Hulbert, 1997). Analogous, but less extreme effects are seen even in salmon, which showed increased oxidative stress on a high n-3 diet (DHA or EPA), and lower mitochondrial cytochrome oxidase activity (Kjaer, et al., 2008).

Maintaining a high rate of oxidative metabolism, without calorie restriction, retards the accumulation of PUFA, and a high metabolic rate is associated with longevity. An adequate amount of sugar maintains both a high rate of metabolism, and a high respiratory quotient, i.e., high production of carbon dioxide. Mole rats, bats, and queen bees, with an unusually great longevity, are chronically exposed to high levels of carbon dioxide. Carbon dioxide forms carbamino bonds with the amino groups of proteins, inhibiting their reaction with the reactive "glycating" fragments of PUFA.

To minimize the accumulation of the highly unsaturated fatty acids with aging, it's probably reasonable to reduce the amount of them directly consumed in foods, such as fish, but since they are made in our own tissues from the "essential fatty acids," linoleic and linolenic acids, it's more important to minimize the consumption of those (from plants, pork, and poultry, for example).

In the resting state, muscles consume mainly fats, so maintaining relatively large muscles is important for preventing the accumulation of fats.

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