Dietary Fat and Health: The Evidence and the Politics of Prevention

Careful Use of Dietary Fats Can Improve Life and Prevent Disease

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ABSTRACT: Every year, more young people start the slow progressive injury that eventually becomes cardiovascular disease and death. It could be prevented with nutrition education, but medical efforts focus more on treatments for older people than on preventing primary causes of disease in young people. Two avoidable risks are prevented by simple dietary interventions: (1) Eat more omega-3 and less omega-6 fats, so tissues have less intense n-6 eicosanoid action, and (2) eat less food per meal to lower vascular postprandial oxidant stress. An empirical diet–tissue relationship was developed and put into an interactive personalized software program to aid informed food choices.

KEYWORDS: essential fatty acids; omega-3; omega-6; polyunsaturated fatty acids (PUFAs); highly unsaturated fatty acids (HUFAs); eicosanoids; thrombosis; inflammation; atherosclerosis; prenylated proteins; platelet activating factor (PAF); oxidized LDL

Much of this chapter echoes talks given 10, 20 and 30 years ago,[1–3] presenting information which failed to percolate effectively into clinical practice or preventive nutrition. As a result, I continue trying to find different methods of effective education so that chronic diseases may be prevented in the elderly. Recent efforts involve two distance-learning web sites with useful "homework" for everyone who wants to learn. One site, for education about essential fatty acids[a] has many details to help people understand the effects of nutritionally essential fatty acids. The other[b] has been hosted by the Office of Dietary Supplements for almost four years, and was upgraded recently with additional background information on how diet affects eicosanoids and how eicosanoids affect health and life.

[a]http://efaeducation.nih.gov/
[b]http://ods.od.nih.gov/eicosanoids/

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The death rate from heart attacks in the United States is among some of the worst in the world.[4] FIGURE 1 demonstrates that death, not life, begins at 40. That is the age at which people begin to lose colleagues and become aware of death. Students feel invulnerable, because not many 30-year-olds die. However, among my peers in their 70s, 1 or 2 per 100 are likely to die of ischemic heart disease in any year.[1] Clinicians say that arterial damage and calcium deposition is just a matter of aging, and that nothing can be done about that. I don't believe that a bit. In Japan, age-specific death rates for coronary heart disease are much lower.[5] However, an apparent inevitability about this is rooted in American lifestyles, all the way back to childhood.

FIGURE 1, presented in 1993,[1] has results added from the PDAY (Pathological Determinants of Atherosclerosis in Youth) study,[6-8] which documented this problem definitively. The problem became apparent 50 years ago, when young soldiers were being killed in Korea. Autopsies showed coronary artery damage in 20-year-old Americans, but not in native Koreans.[9]

Results from the PDAY study[6–8] show that effective primary prevention of atherosclerosis needs to begin with adolescents. FIGURE 1 suggests that by the time American men are 55 years old, most already have inflammatory

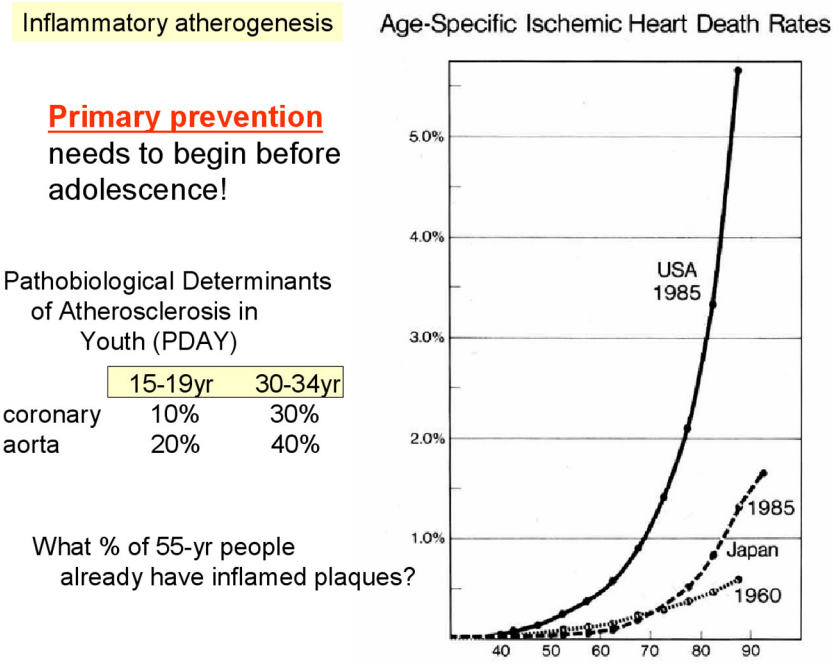

FIGURE 1. Inflammatory atherosclerosis begins developing before adolescence. (Presented in 1993;[1] results added from the PDAY study.[6–8]

plaques in their arteries. Intervention then is really secondary prevention.[10] The effective new technique of electron beam computerized tomography is maturing into a wonderful diagnostic tool.[11] Unfortunately, knowing that you have a lot of calcium in your arteries doesn't tell you how to get rid of it or how to prevent it from accumulating further. We still have a lot of biochemical work to perform.

Real primary prevention doesn't fit programs or goals of pharmaceutical companies, because they cannot make money by preventing the diseases they treat.[10] They work with treatment-oriented groups who aren't interested in educating people about specific dietary interventions that prevent causes of risk. One avoidable risk, an imbalance between intake and expenditure of energy, has received a lot of attention in the last two years. There is a need for further discussion about how it affects vascular inflammation and oxidant stress.

One solution is to eat foods that provide less energy per meal, as noted later in this chapter (FIG. 3). A second avoidable risk is the current severe imbalance between omega-3 and omega-6 nutrients. Most people are completely oblivious to it, but that imbalance is easily corrected by adjusting dietary intakes to more omega-3 and less omega-6 fats. The current imbalance in America is just a happenstance of food marketing.[12] Unfortunately, priorities of corporate health groups will favor the status quo over any action that prevents disease and suffering without adding to corporate profits.[10, 12]

FIGURE 2 shows the consequence of this imbalance. The horizontal axis shows that apparently healthy normal people around the world have different balances of omega 6 and omega 3 in their HUFAs (highly unsaturated fatty acids) because of the different foods they eat.[13,14] The HUFAs are pivotal in the body's healthy self-healing actions. Epidemiology shows that when HUFAs in the body are 70 or 80% omega 6, coronary heart disease rates are around 200 per 100,000.[4] In contrast, people in Spain or Italy have HUFAs containing about 60% omega 6 and 40% omega 3,[10] and their CHD mortality rate is around 120 per 100,000. In Japan, the traditional proportions of HUFAs are about 35–40% omega 6 and 60–65% omega 3, and the heart attack rate in Japan is about one-fourth to one-fifth that in the United States.[5] In Greenland, coronary heart disease is almost undetectable.

Many investigators do not like transnational epidemiology, claiming that genetic diversity impairs interpretation. However, genetic diversity within the United States is probably greater than the mean genetic difference between the United States and Japan. Now we have data from three groups in Quebec, within the same province of the same country on the same continent with the USA. There are urban Quebecois who eat foods that generate HUFA proportions similar to those of people in Chicago and Detroit and New York.[15] On the other hand, in villages north of Quebec City, there are Quebec Cree Indians with different ethnic food habits that give them a different HUFA pattern and mortality rate.[16] Further north in Quebec, Inuits have a lower average n-6

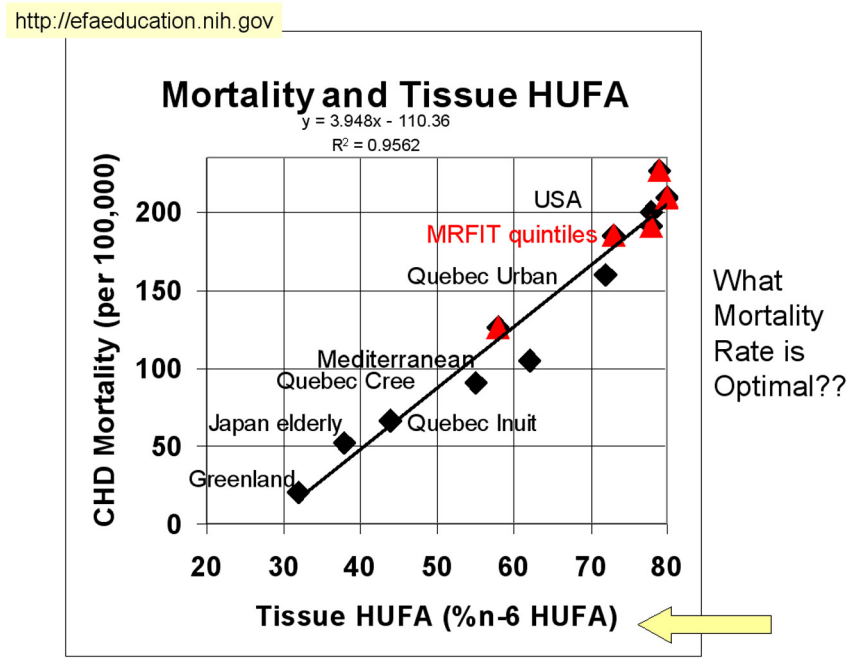

FIGURE 2. Coronary heart disease mortality is proportional to n-6 HUFA in plasma HUFA. Available at <http://efaeducation.nih.gov/sig/personal.html> .

HUFA composition and a lower mortality rate.[17] The trend is clear, even though the Inuit diet has changed tremendously during the last 40 years and is now far more heterogeneous. Indeed, dietary heterogeneity worldwide is the important variable for preventive intervention, more so than genetic variability. Environmental food variability is driving variability in CHD mortality.

Essential fatty acids are polyunsaturated fatty acids (PUFAs) required by all mammals. Like vitamins, these are not produced within the body, and must come from the diet. They are of two types, n-3 and n-6. Linoleic is a n-6 PUFA (18:2n-6) and alpha-linolenic is the n-3 PUFA (18:3n-3). When we eat those acids, our body converts them into longer chain-length, highly unsaturated fatty acids (HUFAs).[c]

What people eat in their diet determines the proportions of HUFAs in their tissue membrane phospholipids. In my first 15 years of academic life, I worked on lipid metabolism[18] and was highly cited on that topic. In 1964, when researchers in Stockholm reported that the n-6 HUFA, arachidonic

[c]http://efaeducation.nih.gov/sig/overviews.html

acid, was converted to the potent hormone, prostaglandin,[19] I hypothesized that HUFA for these hormones comes from the 2 position of the phospholipids in human tissues. But is HUFA converted to eicosanoids on the phospholipids and stored, or is it first hydrolyzed before the free hormone is synthesized? Collaborating with the researchers in Stockholm, I found that the HUFAs in phospholipids were hydrolyzed and then converted to eicosanoids. The hormone then acts at a receptor and generates a signal, which is usually a transient, reversible event that returns to basal state.[20,21]

By the late 1960s, we knew that omega-6 eicosanoids and omega-3 eicosanoids were involved in inflammatory processes. Later, I studied the mechanism by which fatty acid oxygenases act. This requires lipid hydroperoxide activators.[20] Eliminating the peroxides eliminates the ability to make a prostaglandin. Peroxides are also required to activate ribonucleotide reductase, and the free radical is essential to make deoxyribonucleotides for new DNA. The eicosanoids, and the peroxide tone that regulates them, are usually under tight control.[22]

For 15 years I studied aspirin-like non-steroidal anti-inflammatory drugs (NSAIDs),[23,24] working with drug companies to develop new patented drugs for treatment. During the 70s, dozens of eicosanoids were isolated.[21] Nearly all healthy human tissues use eicosanoid modulations of physiologic responses in a rapid transient manner.[20] However, uncontrolled excessive production of omega-6 eicosanoids over prolonged periods of time is associated with heart attacks, thrombotic stroke, arrhythmia, arthritis, asthma, headaches, dysmenorrhea (menstrual cramps), inflammation, tumor metastases and osteoporosis.[21,25] We had been looking at essential vitamin-like fatty acids as "angels" but in excessive amounts they turn into devils. When the body goes out of control, something must be done, and it became my goal to prevent this loss of control.

Two brief narrated presentations covering these general issues are available on the Internet.[d] The distance-learning site for the Office of Dietary Supplements has a section on dietary reference intakes[e] with a graph and citations.[f] These show that most people are eating on the order of 20 times more of the essential vitamin-like n-6 linoleic acid than they need.As with vitamin A and vitamin D, from which the body makes potent hormone-like compounds, there is a probable risk in excessive intakes. The website notes evidence for requiring these substances in amounts on the order of 0.5% of calories or less, but a day's menu in the United States far exceeds that.

To design an effective prevention strategy, one needs to identify causal mechanisms by asking how people die. From this point of view, the role of cholesterol[26, 27] has been portrayed in a misleading fashion for 25 years. Al-

[d]http://efaeducation.nih.gov/sig/beginners.html
[e]http://efaeducation.nih.gov/sig/dietary2.html
[f]http://efaeducation.nih.gov/sig/dri.html

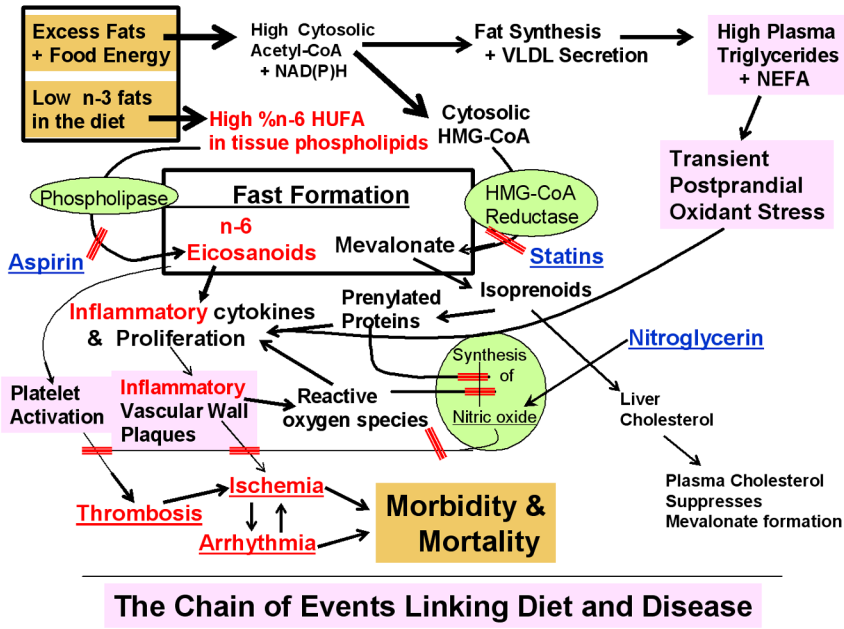

FIGURE 3. Two primary imbalances link diets to disease and death. Modified from an earlier figure[1] at <http://efaeducation.nih.gov/sig/dietdisease.html>.

though some lipoproteins may increase death, cholesterol itself was never proven to kill anyone. However, those who market anti-cholesterol drugs will never mention that fact. To consider primary prevention of heart attacks, we worked backward with the diet–disease concepts shown in FIGURE 3, by stating that a death from heart attack is a death from ischemia, which is exacerbated by arrhythmia, and from thrombosis, which was brought on by a predisposition to inflammatory plaques in the arteries. All three of these processes are exacerbated by n-6 eicosanoids (FIGURE 3). The release of inflammatory cytokines and cell proliferation are enhanced by omega-6 eicosanoids formed from dietary fats.

Inflammatory vascular wall plaques cause ischemia and stimulate thrombosis. Thrombosis is driven by thromboxane, one of the major eicosanoids discovered 29 years ago.[28] Thromboxane causes platelets to clump, causes calcium movement, and causes thrombosis. The omega-6 derivative (TX_{A2}) has the same effect; the omega 3 (TX_{A3}) also has that effect, but to a limited degree.

Aspirin, statins, and nitroglycerin are used widely to diminish the processes set in motion by the two nutritional imbalances shown in the upper left of FIGURE 3. In 1979, when I lectured[2] about these issues in Switzerland and the

Netherlands, the socialized medicine systems in those countries were paying for expensive coronary bypass surgery, and governments were considering preventive nutrition as an economic measure. However, proponents of medications and surgery were not interested in what they regarded as nutritional behavior modification. I scorned the clinicians' disinterest in nutrition at the time, but now I see they may be right. Often it is easier to persuade people to have surgery than to persuade them to change their ideas about what to eat.

What can we do to change people's behavior? Our responsibility is to inform people properly, and their responsibility is to learn what we are trying to teach. The two dietary interventions that people need to learn are shown in the upper left-hand corner of FIGURE 3. Eat more omega-3 and less omega-6 fats to have less-intense n-6 eicosanoid actions. Also, eat less high-energy food per meal to cut transient postprandial oxidant stress three times a day, a thousand times a year. Even when it's 99.9% reversible, the remaining one-tenth of a percent creates another irreversible inflammatory locus every year. By the time people are in their 70s, and the postprandial stress has excess n-6 HUFA and pro-inflammatory eicosanoids, then their condition is seen to move downward in FIGURE 3 and upward in FIGURE 1.

Low-density lipoprotein (LDL) and its phospholipids have some effect on events in FIGURE 3. When inflammatory sites oxidize those phospholipids, they create a platelet activating factor (PAF) agonist that binds the PAF receptor, causing calcium influx plus a stronger inflammatory response. That process has been understood, published, and well accepted for a decade. PAF and PAF mimics are potent calcium ionophores and inflammatory agents in mammalian tissue.[10] Electron beam computerized tomography, described in this volume by Dr. Harvey Hecht,[11] gives a good measure of atherosclerosis by measuring calcium accumulation. We need to learn more about what causes calcium to accumulate and how to prevent it and reverse the effect. Like LDL, high-density lipoprotein (HDL) is an aggregation of proteins, some of which are anti-inflammatory enzymes that destroy PAF and the oxidized phospholipid, preventing them from causing calcium entry and inflammation.[10]

Membrane phospholipids are limited in abundance, and the HUFAs compete for the limited space. If you eat a lot of n-6 fat, it displaces n-3 HUFAs and enhances n-6 eicosanoid formation (FIG. 3). If you eat a lot of n-3 fat, it displaces n-6 HUFAs. The enzymes are promiscuous and don't discriminate much between n-3 and n-6 HUFAs, which means that what you eat can change your body tissue.[13,14]

In the mid-80s, after a Nobel Prize had been awarded for discovery of eicosanoids and their physiology and I had done years of research on lipid metabolism and on NSAID mechanisms, it was well-know that n-6 thromboxane caused heart attacks and n-6 prostaglandins caused inflammation.[25] Pfizer gave me a grant to study the relationship between dietary n-6 and n-3 fats and the proportions of n-6 HUFA in body tissues. I developed and published an empirical predictive equation.[13,29]

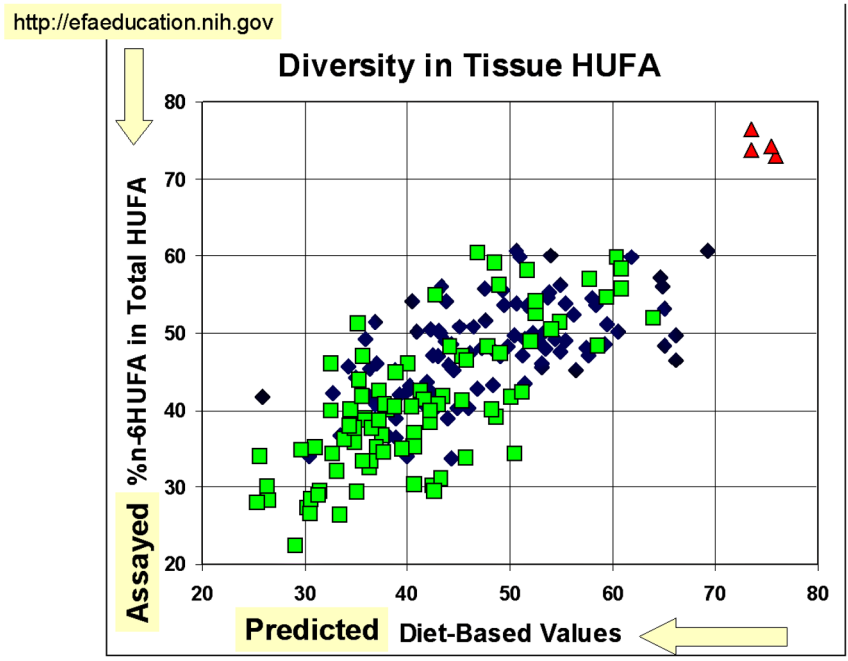

FIGURE 4. Predicted proportions of HUFA fit observed proportions. Previously presented[5] in 2003.

Sadly, I don't think many people read those papers, and I don't think anyone used the equation.[g] I then put it into a spreadsheet so people are not required to do any algebra. They can simply put numbers into a table and let the spreadsheet calculate the likely outcome.[h] FIGURE 4 shows that the equation predicts outcome with a correlation coefficient greater than 0.95. Dietitians carefully monitored the food that people ate, and that information inserted into the equation predicted values of the percentage of n-6 HUFAs in the total HUFA value. There is a good fit between predicted HUFA proportions and those observed by gas chromatographic analysis.[5]

The vertical scatter may be due to proteomics and genomics, whereas horizontal scatter is likely due to imprecise interviews. The group of people represented in the upper right hand in FIGURE 4 were 35-year-old Chicago women. The diamonds represent a group of 45-year-old dietitians in the cities of Japan, and the squares show 55-year-old rural Japanese men. They are all healthy people eating what they choose. The mean value for all people in ei-

[g]http://efaeducation.nih.gov/sig/hufacalc.html
[h]http://efaeducation.nih.gov/sig/dietbalance.html

ther FIGURE 4 or FIGURE 1 would not reveal much about any individual value or the risk of any individual in the group. Those who ate more dietary n-6 as linoleic acid (of which Americans eat a lot) acquired predictably higher proportions of n-6 HUFAs.[13,30]

I used the Pfizer grant to develop a diet–tissue relationship because people doing clinical interventions were making ineffective changes in the diet, too little and too late. Now you can sit down and plan effectively with a little "pocket calculator" at the learning site.[j] The outcome depends on four kinds of dietary essential fatty acid: the 18 carbon n-3 and n-6 and the long-chain n-3 and n-6 HUFA. Diet–tissue calculations can now be handled in a simple spreadsheet, using no algebra or arithmetic.

To illustrate the diet–tissue relationship, the family of curves in FIGURE 5 indicate how different mixtures of n-6 linoleate and n-3 HUFA in daily food create tissue HUFA proportions. Four different ethnic groups are shown as ovals. We still have a long way to go from the HUFA status for average Americans (200 deaths per 100,000 people) to where we might like to be. One cannot choose one's parents or one's genetics, but one can choose the food one puts in one's mouth.[30] It's a simple intervention for someone who is properly informed.

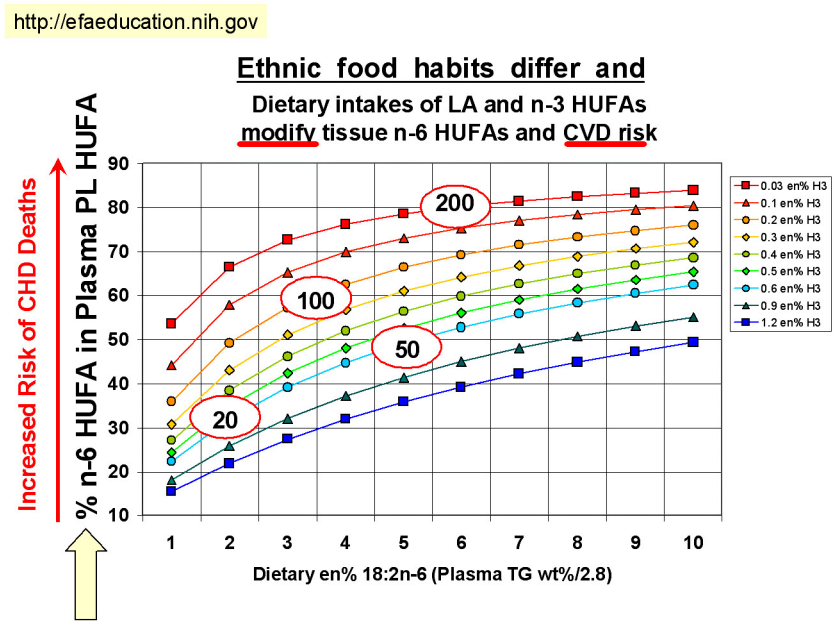

FIGURE 5. Diet–tissue relationship predicts the tissue proportions of n-6 HUFA in tissue HUFA. Available at <http://efaeducation.nih.gov/sig/food2.html>.

[j]http://efaeducation.nih.gov/sig/dietbalance.html

The HUFA proportions for 3,000 Quebec residents ranged from 15 to 91% n-6 HUFA. From FIGURE 2, people can choose their comfort level: what HUFA value they would like to have, and what heart attack risk they would accept. Many people don't want to choose; they want to be told the optimum value. FIGURE 2 makes it obvious that there is no optimum. As you go to higher proportions of n-6 HUFA, the risk grows worse.

Others can see the relationship and risk, but they want to be told which foods are best to eat. Although the distance-learning sites provide a great deal of background information, I decided to use the USDA data base of 6,000 different foods, more than 12,000 servings of food, to create an interactive, computerized, personalized, daily menu-planning program that can be downloaded free.[k] The program allows users to choose foods they want to eat, and it keeps the data managed to let them see whether the daily totals meet their personal goals of cardiovascular risk. The food software takes lifestyle information and tells users what their recommended daily energy allowance is (a value that most sedentary Americans exceed).[31] It also gives some background concepts of risk, and then asks users to choose their risk level and begin choosing foods. Once they look at specific foods, they can begin to see where the omega 6 is entering their diet. For example, the software tells users that the USDA describes a serving of applesauce as having 583 milligrams of 18-carbon omega-6 and only 48 milligrams of omega-3 with no long-chain HUFAs. You can't find any food that doesn't have quite a few milligrams of n-6 linoleate. People producing foods put in n-6-rich oils and raise the level even higher; some breads and muffins have huge amounts. The interactive software shows details and gives the bottom line—total daily total calories and the likely surrogate outcome of HUFA proportions. It also gives a few other dietary facts that dietitians are concerned about and want to convey.

What people really need to know is that their caloric intake is correct and their proportions of eicosanoid precursors are where they want them to be. The nature of a mealtime is that people eat more than they need at that moment and then have transient excess. That excess and its transient postprandial oxidant stress is the beginning of a problem.

If people ate only one meal a day, they would have a large bolus of carbons and electrons entering metabolic pathways. The liver would to make free radicals (and also make cholesterol) and the endothelial cells would respond with oxidant stress due to that postprandial bolus. If people ate smaller meals, five times a day, they would have smaller and more reversible oxidant stress; it would be still lower, with more n-3 and less n-6 HUFAs in the tissues. To take in less energy per meal, people should eat several small meals or snacks if they want. One of the underlying rules is to eat no more than you need.

The top predicted causes of death and disability[32] worldwide for 2020 (ischemic heart disease and unipolar major depression), and three top causes

[k]http://efaeducation.nih.gov/sig/kim.html

in developed regions (ischemic heart disease, cerebrovascular disease, and unipolar major depression) all seem linked to imbalanced omega-3 and omega-6 actions in tissues. We knew about n-6 eicosanoid mechanisms for thrombosis and inflammation 25 to 30 years ago. In the past five years, increasing evidence suggests that major depression, post-partum depression, and behavior disorders also relate to imbalances in omega-3 and omega-6 dietary intakes. Additional evidence showed important actions of n-3 HUFAs in brain function,[33] and the American Heart Association recently urged putting more n-3 HUFAs into daily diets.[34] The growing awareness of the importance of balancing n-3 and n-6 fats is evident from the single major personal health change recommended recently by the health and nutrition division members of the American Oil Chemists' Society: to eat more fish and take an omega-3 supplement.[35] Also, their most frequent advice to other people was to eat more seafood and fish.

In this volume, Dr. Richard Cutler[36] has given us a philosophical view of these issues. We tend to simplify matters that are complex. We use words like "gene" or "the genome" or "inflammation" or "aging," as if these phenomena were a single entity when, in fact, they are a mass of ill-defined parts. On the other hand, some things that are actually simple seem complex. FIGURE 3 outlines the chain of events that lead from food choices to morbidity and mortality. Three types of medication (aspirin, nitroglycerin, and statins) are noted, to show the step in the process at which these familiar drugs intervene. However, when we recognize the initial imbalances in our nutrition that cause cardiovascular death, we can design more effective primary prevention and better nutrition education for the public.

Inflammation was always important in vascular disease, and it was driven by excessive n-6 eicosanoid actions amplifying results of excessive food energy, producing more carbon and electrons than the body could deal with at any given moment. That led to increased cytosolic acetyl-CoA and HMG-CoA, which led to more mevalonate and prenylated proteins (FIG. 3) which are having effects that we didn't recognize 20 years ago. Some prenylated proteins block synthesis of nitric oxide and enhance inflammation. They come about because HMG-CoA reductase is pushed into making more mevalonate than necessary. We knew 25 years ago that plasma cholesterol gave negative feedback that suppressed cholesterol biosynthesis. We subsequently learned that plasma cholesterol suppresses the proteolysis of sterol regulatory element-binding protein, slowing activation of genes expressing fat-forming enzymes. The misimpression that cholesterol (a marker of excessive HMG-CoA reductase action) has been killing people, when the killers are actually vascular inflammation, thrombosis and arrhythmia, is one of the tragedies of biomedical science.[26,27]

The discussion in FIGURE 3 notes that lipoprotein (LDL) has phospholipids that form highly potent inflammatory agents on oxidation, regardless of cholesterol. Phospholipids in the LDL may be deadly. HDL may have cholesterol

(and it has phospholipids), but it has enzymes that neutralize inflammatory oxidized phospholipid PAF mimics and PAF.[37] So HDL is beneficial and LDL is harmful, but it's absurd to talk about "bad cholesterol" and "good cholesterol." We can hope that the tragic detour that delayed understanding of nutritional causes and preventive interventions is nearly over, and that the organizations that could provide the necessary information will do so. Then a new day will dawn for the young people in whom every successive year perpetuates the slow progressive injury that leads to cardiovascular disease and death.

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