

## FUNCTIONAL FOODS IN PRIMARY PREVENTION OR NUTRACEUTICALS IN SECONDARY PREVENTION?

William E.M. Lands

6100 Westchester Park Drive, College Park, MD, 20740 USA

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**ABSTRACT:** *Scientists used knowledge of the metabolic links of dietary essential fats to chronic disease and death to develop billions of dollars of successful pharmaceutical treatments, but they failed to translate the science into policy options that prevent the risk factors from emerging in the first place. A high proportion of omega-6 eicosanoid precursor in the highly unsaturated fatty acids (HUFA) of tissue phospholipids supports overly vigorous formation and action of omega-6 eicosanoids in mechanisms that contribute to cardiovascular disease and death. The risk factor for this major worldwide killer is closely associated with observed mortality rates and is predicted from daily intakes of essential fatty acids. Voluntary food habits provide different individuals with proportions from 20 to 80 % omega-6 HUFA in tissue HUFA, greatly modifying the intensity of tissue omega-6 eicosanoid responses. This risk factor from present food choices can be modified easily by individuals carefully choosing available foods, by making new functional foods available to the public, or by providing nutraceuticals to identified patients. Are scientists ethical to withhold community-wide primary preventive nutrition procedures and only give treatment to diseased individuals in whom clinical signs appear?*

**KEY WORDS:** Autacoid; Cardiovascular; Eicosanoid; Essential fatty acid (EFA); Highly unsaturated fatty acid (HUFA); Omega-3; omega-6; Phospholipid; Prevention

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*Corresponding Author: Dr. William E. M. Lands; 6100 Westchester Park Drive, College Park, MD, 20740 USA; Telephone/FAX, 1-301-345-4061; email, wemlands@att.net*

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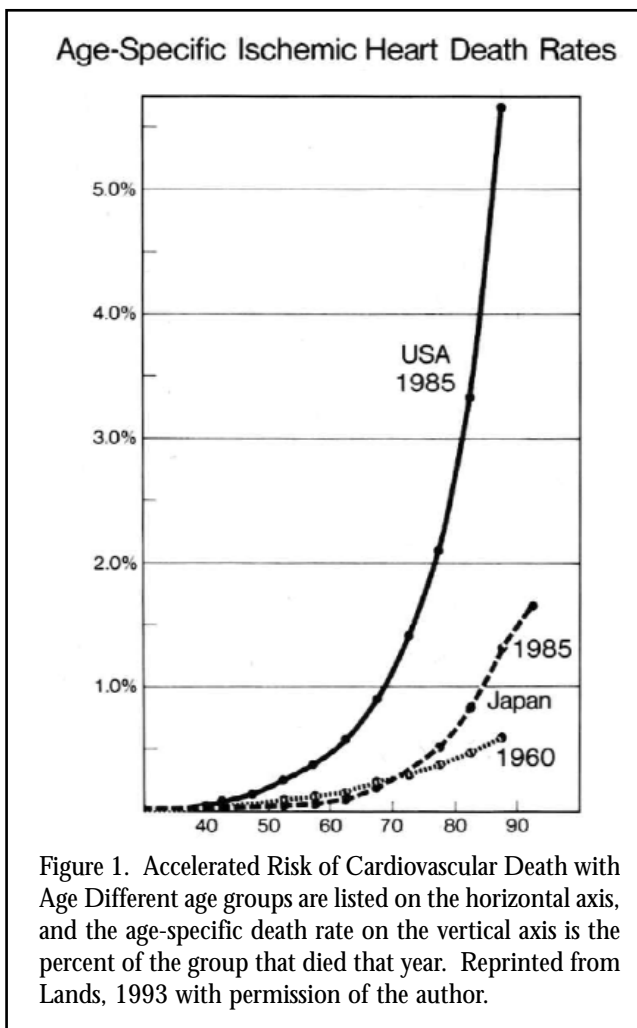
### TRYING TO HELP PEOPLE

The word nutraceutical stirs the imagination and brings ideas about successful pharmaceutical therapies that have been developed to treat diseases and prevent deaths. One can easily imagine a nutraceutical being prescribed by a doctor for a patient with a problem. However, for every successful therapeutic/curative treatment that decreases clinical signs and symptoms, we can ask, "Did removal of the clinical signs also remove the original underlying cause of the disease?" Among

the causes of cardiovascular disease (and many chronic diseases of the elderly), much evidence points to nutritional imbalances in expenditure/intake of energy and in omega-3/omega-6 essential fatty acids (Lands, 1993). The nutritional imbalances that alter tissue composition and function can easily remain in lifestyle habits of individuals even after treatment/curative procedures have suppressed the diagnostic clinical signs and symptoms. More importantly, these causal imbalances usually act chronically over decades before the clinical signs become easily observed and before the person becomes a "patient" to be treated. As a result, even before people become patients, nutraceuticals are probably important. Could the underlying nutritional imbalances be prevented BEFORE clinical signs bring the person into the category of "patient" to be treated by a doctor? If daily food choices give inadequate composition and function of tissues, then a functional food may add the needed component to maintain health and prevent clinical signs of disease. However, if neglect of primary prevention permits disease to develop in a population, health care professionals may prescribe pharmaceutical or nutraceutical treatment and secondary prevention for affected individuals. An important ethical issue relates to the difference between primary and secondary prevention. Is it ethical to withhold community-wide preventive nutrition procedures and only wait until after disease signs appear in individuals who may then be treated to remove the signs but not the initial causes? A dismal thought is that nutraceuticals may be just functional foods that are used too late to prevent the onset of disease.

For cardiovascular disease and death, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group gave conclusive evidence of the inexorable progress of vascular damage for which early prevention procedures need to begin with children and adolescents (PDAY group, 1990). Autopsy showed fatty streaks in abdominal aortas of about 20% of 15- to 19-year-old subjects and nearly 40% of 30- to 34-year-old subjects. Raised fatty streaks were present in the right coronary arteries of nearly 10% of 15- to 19-year-old subjects and approximately 30% of 30- to 34-year-old subjects (McGill et al., 2000). The onset and progression of vascular damage is usually well established before the ages of

forty or fifty when fatal signs of cardiovascular disease begin to appear as a statistically significant problem. With the rate of progression of vascular damage predicted by the existing number of plaques, the explosively accelerating curve of age-adjusted death rates with age brings death with greater certainty with advanced age. The probability of becoming a centenarian in the USA is low compared with Japan. Figure 1 shows clearly that the age-adjusted risk of dying from ischemic heart disease is lower for elderly Japanese than elderly Americans (Lands, 1993). However, it also shows a hint that death rates may be changing in Japan in an undesirable manner over the past decades.



Evidence of changing imbalances in energy and essential fatty acids suggest that worse times may be coming for the Japanese population if stronger prevention efforts are not made soon (Lands et al., 1990). Does a greater good lie in a priority to prevent clinical signs of disease from occurring in the whole population rather than in a priority to treat clinical signs of disease only AFTER they become obvious in individuals? Because preventing nutritional imbalances in a population goes beyond traditional curative/treatment procedures used to suppress clinical signs in individuals, a difficult unanswered question about nutrition-based diseases is "What

group of professionals, what type of corporation, and what government agency will take responsible successful actions to prevent them from occurring?"

#### LINKS BETWEEN DIET, TISSUE, DISEASE AND DEATH

Conversion of omega-6 essential fatty acids into hormone-like autacoids (auto=self; akos=healing) called eicosanoids is involved in sudden death with thrombosis and arrhythmia, as well as in the chronic inflammatory atherosclerosis that predisposes vascular systems to those fatal mechanisms. Pharmaceutical agents that decrease excessive action of omega-6 eicosanoids are some of the most widely used medications worldwide. Nearly everyone has seen use of a non-steroidal anti-inflammatory drug (like aspirin) to relieve suffering from excessive omega-6 eicosanoid actions. Many well-advertised drugs decrease the excessive formation and action of omega-6 eicosanoids not by supplementing some deficiency of that unnatural drug, but by inhibiting mobilization of autacoids from an imbalanced store of natural precursors. Clearly, the drugs give a health benefit in decreasing excessive omega-6 eicosanoid action, even when the underlying nutritional imbalance that helped cause the disease remains. However, any patients who stop these medications are at risk of likely needing more medication soon. Unfortunately, current extensive (and expensive) pharmaceutical marketing does not inform the public that the sole source of the omega-6 eicosanoids formed during tissue responses is the essential fatty acids in the foods that people eat. Also overlooked is the basic fact that competition between omega-3 and omega-6 acids occurs while dietary essential fatty acids (EFA) are metabolized and stored in tissue membranes as highly unsaturated fatty acids (HUFA). As a result, decreased intakes of omega-3 fats raises the proportion of omega-6 forms in tissue HUFA, whereas increased intakes of omega-3 fats decreases the proportion of omega-6 forms in tissue HUFA (Lands, 1995). This competitive balance in tissue HUFA sets the stage for pathological excessive omega-6 tissue responses in atherosclerosis, thrombosis, and arrhythmia and its diminution by dietary omega-3 fats. Here is a situation in which nutraceuticals can serve in secondary prevention of CHD for patients with known problems whereas foods or functional foods can serve to prevent developing disease signs before they occur.

Thirty years ago, I made unsuccessful efforts to educate pharmacologists about how dietary omega-3 fats go into tissue lipids where they act as "resident drugs", displacing omega-6 acids and decreasing omega-6 eicosanoid actions (Lands et al., 1973). The corporate researchers told me that their goal was to create patented drugs to treat diseases rather than wasting time on unprofitable, unpatented nutrients, and they advised me to talk to food marketers. Then, after Karolinska researchers taught us all that thrombosis is caused by excessive actions of the omega-6 eicosanoid, thromboxane A<sub>2</sub> (Hamberg et al., 1975), I made unsuccessful efforts to educate cardiac surgeons and cardiologists about the dietary

origins of the omega-6 autacoids mediating sudden death (Lands et al., 1980). They told me that they would consider prescribing aspirin-like drugs for their patients (a quick and profitable action), but prescribing food changes would be a "behavior change" protocol for which they felt no interest or responsibility. When I then made unsuccessful efforts to educate food marketers, they told me that their profits lay in giving the public a sense of pleasure in eating foods rather than disturbing them about omega-6 mediated diseases and deaths. Furthermore, many food companies were at that time oriented toward promoting more intake of polyunsaturated fats that were mostly omega-6 fats. There was little interest by any major organization in the role of dietary omega-3/omega-6 balance as a causal factor in cardiovascular death. Ten years ago, I hoped that discussions with cardio- and cerebrovascular researchers in Japan (Lands, 1993) would lead to some useful implementation of cardiovascular disease prevention, but it didn't because organizing preventive implementations is not in the immediate interests of a researcher curious about discovering new phenomena or a clinician biased toward treatment of existing disease. Apparently, no organization sensed profit in primary prevention, and it was not implemented.

Now, we are twenty years past the award of the Nobel Prize for research on eicosanoids and much is known about the self-healing autacoid actions and the harmful consequences of

their overproduction. Unfortunately, there is still little receptive interest by any major organization in preventing the omega-3/omega-6 imbalance that contributes to cardiovascular death (as well as many other devastating diseases). The normal conversion of tissue HUFA to hormone-like autacoids during tissue responses to challenge usually gives reversible healthy actions. However, repeated excessive omega-6 actions can result in irreversible pathology. Figure 2 shows the strong association of cardiovascular mortality to the proportion of omega-6 HUFA in tissue HUFA. The figure also illustrates the wide diversity with which different populations are already voluntarily engaged in primary prevention of disease and death. Food choices can cause proportions of omega-6 HUFA in plasma phospholipid HUFA to differ from 20 and 80%. Although four quintiles of participants in the MRFIT clinical trial maintained proportions above 75% omega-6 in HUFA (squares in Figure 2), the quintile eating the most seafood was near 60% with about one half the relative risk of CHD death (Dolecek and Grandits, 1991). People whose food choices put them at the upper right might be expected to be interested in choosing foods, functional foods, and nutraceuticals that can move them toward the left and downward in risk. Similarly, populations at the lower left may wish to set prevention policies that help their communities resist global marketing pressures that shift tissue proportions toward the right (with a resultant rise in CHD risk).

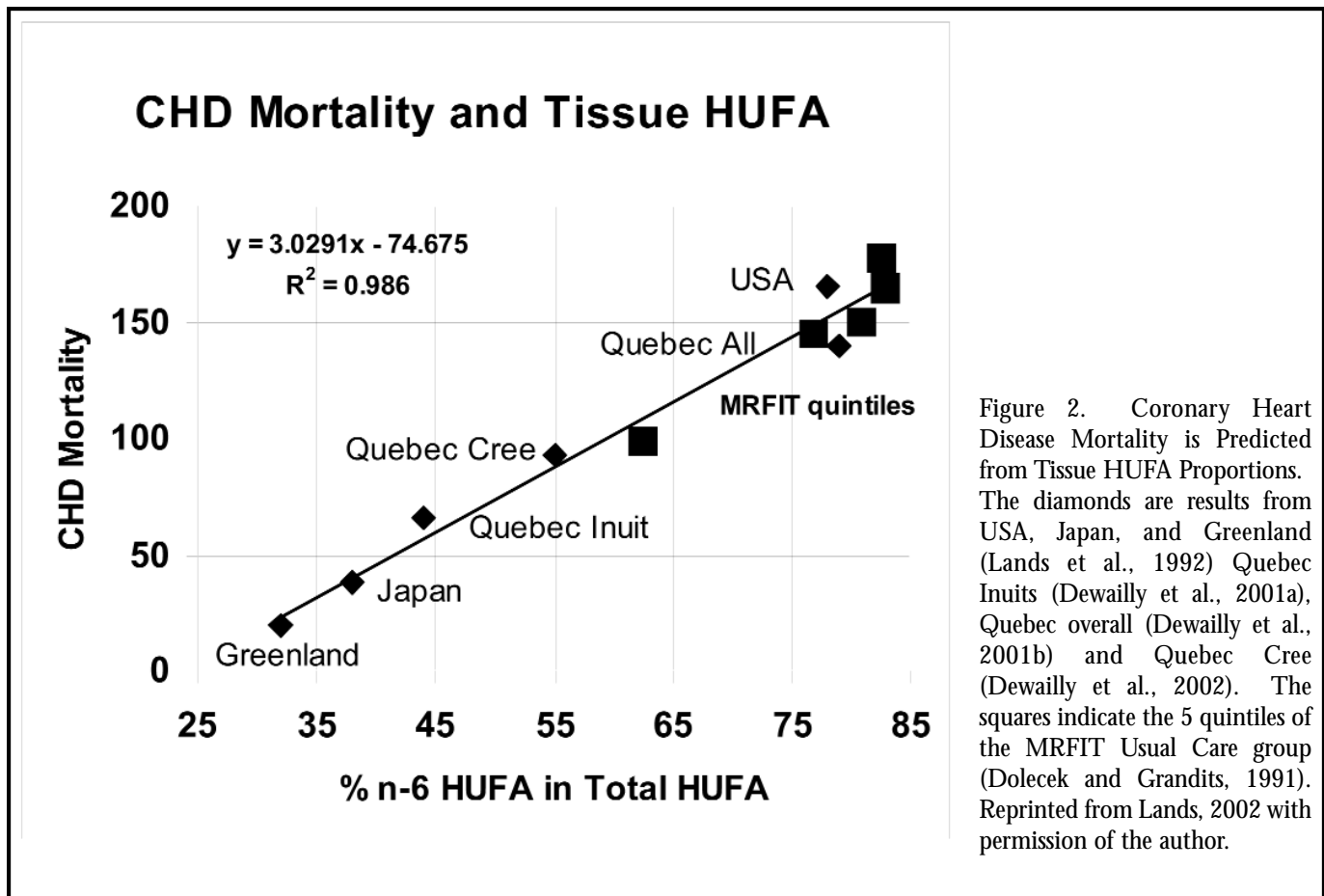


Figure 2. Coronary Heart Disease Mortality is Predicted from Tissue HUFA Proportions. The diamonds are results from USA, Japan, and Greenland (Lands et al., 1992) Quebec Inuits (Dewailly et al., 2001a), Quebec overall (Dewailly et al., 2001b) and Quebec Cree (Dewailly et al., 2002). The squares indicate the 5 quintiles of the MRFIT Usual Care group (Dolecek and Grandits, 1991). Reprinted from Lands, 2002 with permission of the author.

### PREVENTING A PROBLEM

To succeed in designing an effective nutritional approach to preventing unwanted imbalances in tissue HUFA that give excessive omega-6 eicosanoid actions, people need to understand the quantitative diet-tissue metabolic relationship that causes these conditions. The competitive hyperbolic interactions connecting the abundant dietary EFA (18:2n-6 and 18:3n-3) to tissue proportions of HUFA (20:3 +20:4 +22:4 +22:5n-6 and 20:5 +22:5 +22:6n-3) are predicted by empirical equations (Lands et al., 1992) as shown for Americans in the upper right corner of Figure 3. Each of these four types of EFA in the diet (n-3 and n-6 18-carbon EFA and n-3 and n-6 HUFA) combines to maintain predictable proportions of omega-3 and omega-6 HUFA in the tissue HUFA. Figure 3 shows diverse individual food habits result in tissue HUFA proportions assayed by gas chromatography of plasma fatty acids that agree with the proportions predicted from careful nutrient assessment entered into the hyperbolic equation. The higher mean value among Japanese 47-year old urban nutritionists (Kuriki et al., 2002) relative to the 57-year old rural Japanese (Kobayashi, M. et al., 2001) likely illustrates the steady shift in Japanese food choices over the past decades as younger, urban individuals eat foods other than traditional Japanese foods.

The US-Japan Malnutrition Panel (Lands et al., 1990) described patterns of food in Japan changing in 1990 toward more n-6 EFA intake, with Japanese high school students

starting to eat foods similar to that of Americans. At the time, there was clear warning of a rising risk of omega-6 eicosanoid-mediated diseases in Japan as food habits change. Now, Figure 4 shows how the proportions of omega-3 and omega-6 acids in the plasma HUFA for younger Japanese cohorts have clearly higher proportions of omega-6 eicosanoid precursors as the food habits of younger Japanese have shifted the relative intakes of dietary EFA (Kobayashi, T. et al., 2001). Japanese college freshmen had a higher mean proportion of n-6 HUFA in plasma HUFA (60%n-6) than the three year older seniors (58%n-6), and both groups in their twenties had higher n-6 proportions than urban 39-year olds (50%n-6), 46-year olds (45%n-6), 56 year-olds (43%n-6) and the rural 57-year olds (35%n-6). The present cohort of older Japanese seems to be voluntarily maintaining good preventive nutrition that supports centenarians. However, considering Figure 4 in the context of Figures 1 and 2 suggests that if the younger Japanese continue their current eating habits, the incidence of cardiovascular death in Japan will rise steadily over the next fifty years as the younger individuals approach 80 years in age, and the number of centenarians will likely fall. Some preventive intervention to stop the steady drift in imbalanced nutrition seems appropriate.

Two different strategies can help people avoid excessive proportions of omega-6 acids in tissue HUFA; increased intake of competing omega-3 fats and decreased intake of omega-6 fats. Both occur in diverse voluntary ethnic food choices worldwide. Japanese people displace omega-6 from tissue HUFA by

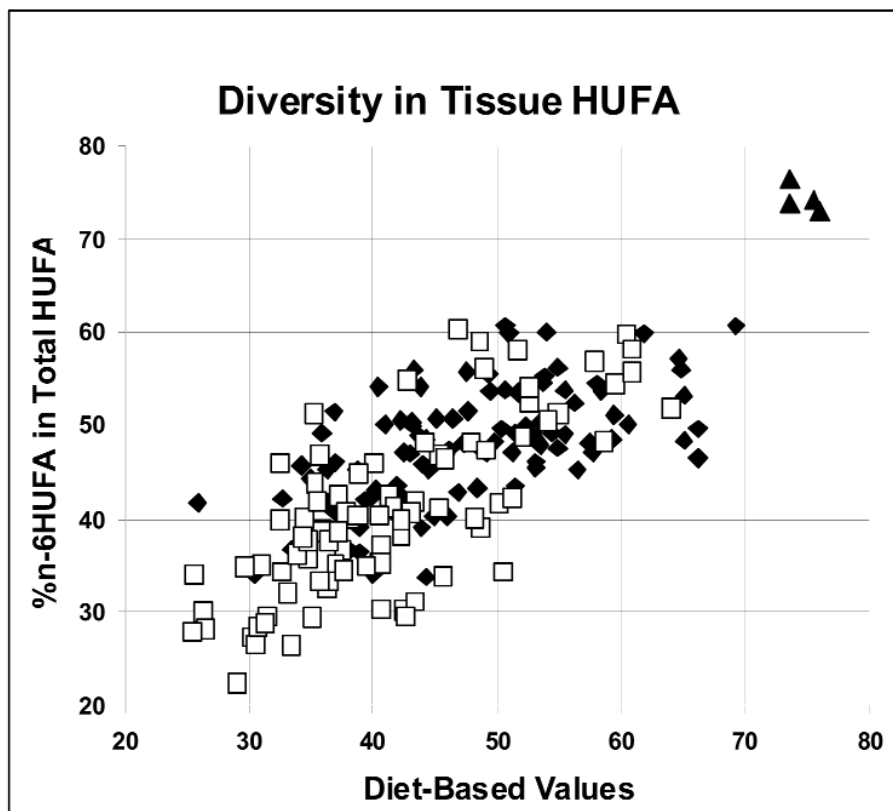


Figure 3. Agreement of Predicted and Observed HUFA Proportions Results are from USA (Lands et al., 1992) in triangles, Japanese rural 57-year olds (Kobayashi M. et al., 2001) in squares, Japanese urban dietitians (Kuriki et al., 2002) in diamonds.

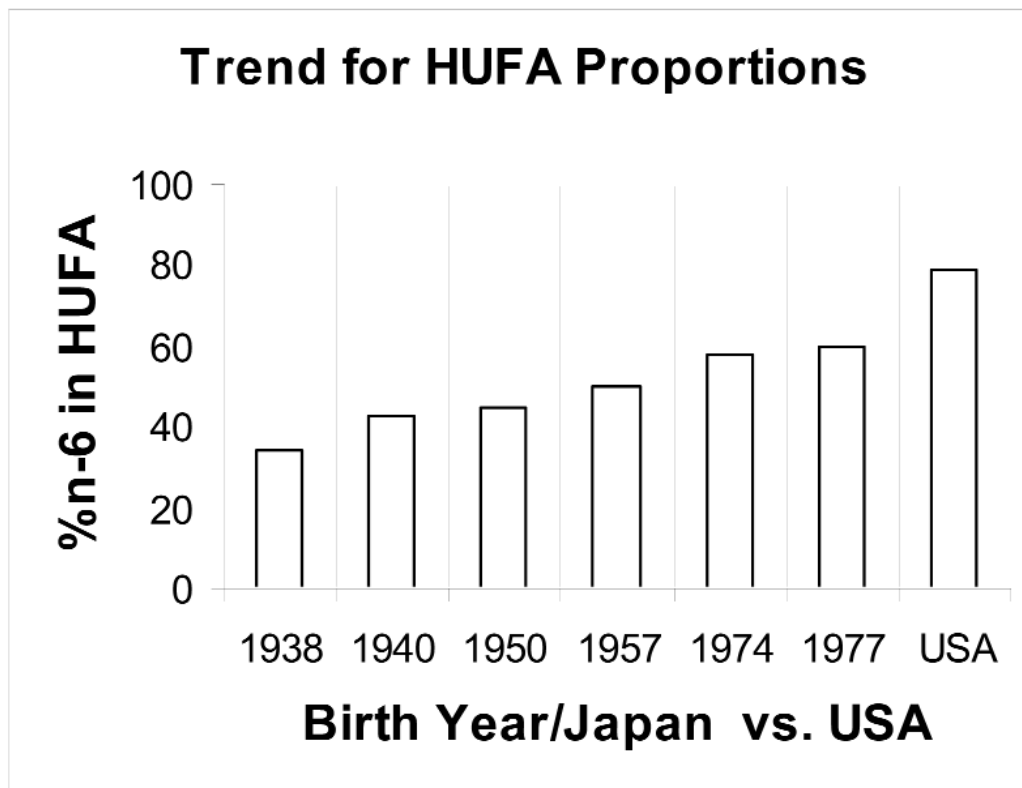


Figure 4. Trends in Tissue HUFA of Japanese

Results are from Kobayashi, M. et al., 2001; Kuriki et al., 2002; Kobayashi, T. et al., 2001; and Lands et al., 1992.

eating amounts of omega-3 HUFA in seafood above the worldwide average, whereas Mediterranean people maintain low proportions of omega-6 in tissue HUFA with smaller amounts of seafood while eating olive oil that has much less omega-6 linoleate than soybean oil. Nutraceutical supplements of 1g/day of omega-3 HUFA benefited cardiovascular patients of the GISSI clinical study in Italy as a form of secondary prevention (GISSI, 1999). The pervasive metabolic competition between omega-3 and omega-6 fats suggests that further benefit might have been obtained with further lowering of linoleate intake. This consideration seems important for Japanese wishing to use nutraceutical omega-3 fats, which must compete with the high average intake of linoleate in typical Japanese diets (about 4.5% of food calories). Decreasing the amount of dietary omega-6 linoleate will likely allow lower intakes of omega-3 fats to keep tissue HUFA proportions in the traditional range of low risk and prevent the explosive accelerated age-specific heart attack mortality rates seen with the USA population. Unfortunately, the biomedical community has neglected to weigh the evidence (Lands, 2002) that linoleate competes so vigorously for the metabolic enzymes that its half optimal value is near 0.05% of food energy (Hansen et al., 1963; Mohrhauer and Holman, 1963; Lands et al., 1992). As a result, eating only 0.5 % food energy as the omega-6 linoleate is fully adequate (Cuthbertson, 1976) to supply the tissue HUFA needed for normal autacoid processes. This low intake acting in the hyperbolic pattern of saturable enzyme reactions (Lands et al., 1992) makes most daily intakes of linoleate highly competitive in maintaining

omega-6 HUFA in tissue HUFA and supporting vigorous omega-6 eicosanoid responses. Successful preventive nutrition must consider not only the relative deficit of dietary omega-3 fats that can be corrected by supplementation, but also the relative excess of dietary omega-6 fats that will resist competition by any added omega-3 fats.

An interactive personalized computer program was developed to facilitate quantitative estimates of how different foods give very different proportions of HUFA in body tissues. Such software combines information on a person's daily food choices and predicts the likely resultant tissue HUFA proportions, which are biomarkers for essential fatty acid intake as well as surrogate clinical markers related to the probable intensity of an eicosanoid response. The software, downloadable free from <http://ods.od.nih.gov/eicosanoids/>, uses the US Department of Agriculture Nutrient Database and manages quantitative information about the essential fatty acids and calories in over six thousand different servings of food. Many foods do not have appreciable amounts of omega-3 fats, and the process of discovering which foods have relatively higher proportions of omega-3 acids is made easier with a computerized "sort" command. Experience with the daily menu planning software makes it very evident that there is a great opportunity to develop and make available a much wider variety of functional foods that will help people balance EFA intakes and create tissue HUFA proportions that they desire. Figure 2 makes it immediately evident that there is a broad continuum of possible HUFA proportions that people might achieve. None is

perfect, and nearly all have less CHD risk than the median value for Americans in the upper right corner.

#### FACING A CHALLENGE

A continuing challenge for Japanese people will be in finding the foods, functional foods, and nutraceuticals that give them the tissue HUFA balance, health maintenance, and disease prevention that they desire. The globalized marketing of foods by large international corporations increasingly moves people toward a worldwide convergence of eating patterns at the same time that the global industrial health care sector is skewing health policy agendas towards curative/treatment issues and ignoring people's ethical right to good health promotion and disease prevention. The emphasis on curative issues and expensive technology seems to favor higher educated people with higher income and leave at high cardiovascular disease risk those least likely to comprehend and reduce their risks. The worldwide right of people to good food and good health needs better implementation, and the scientific knowledge about omega-3 and omega-6 fats needs careful review and translation into health policies for foods, functional foods, and nutraceuticals.

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#### CONFLICT OF INTEREST DISCLOSURE

The author is now retired and serves on the Board of Directors of Omega Protein. Pfizer funded development of the empirical metabolic diet-tissue relationship hosted on a distance-learning-site (<http://ods.od.nih.gov/eicosanoids/>) by the NIH Office of Dietary Supplements.

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