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Measuring Blood Fatty Acids as a Surrogate Indicator for Coronary Heart Disease Risk in Population Studies

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First ... Do No Harm

Medical schools train clinicians to recognize signs and symptoms of severe disease to better care for patients. Observed signs help diagnose and define the disease for which approved treatment interventions may exist. However, a precept in medicine is that doctors should treat the cause of disease, not merely symptoms experienced by the patient [1]. Removing a symptom without removing its cause creates a false sense of health and unethically allows disease to continue undetected and unchecked.

Observed signs or factors that consistently associate with ill health and impending death help predict a person's likelihood (risk) for future harm even though the signs may not cause the harm. For example, greater age, gray hair and wrinkled skin are readily observed surrogates (risk factors) in predicting a shorter than average time to death, but they are not causal factors in the process. As a result, making such factors less visible does not lessen the underlying causes of an earlier death. Clinicians must carefully examine which risk factors are valid surrogate endpoints to use during attempts to decrease disease [2]. Unfortunately, hearsay often replaces logical inferences in the busy schedule of a clinician, and imprecise information spreads widely (illustrated by imprecise attributions to Hippocrates [1]).

Most people want to know their likely risk of disease or death, even though many make inadequate efforts to avoid disease. Motivation to avoid harm can be stronger when a person sees evidence that their personal action can effectively remove a cause of disease or death. A challenge in maintaining health is in knowing primary cause(s) that can be removed. Uncertainty about causal targets can give ineffective preventive efforts that allow continued harmful conditions.



Knowing the molecular connections by which a dietary cause connects to a health consequence helps focus on effective removal of the primary cause and its unwanted consequences. Molecular connections help define whether a sign used in diagnosis is a causal mediator to be removed or is only a parallel associated consequence of causal mediators. Sometimes, treatments removing associated consequences may slow progression of the disease in a form of secondary prevention. However, removing the primary cause is likely to give more ethical, effective and economical long-term results. Over the long-term, the public gains much more from primary prevention of causes than from secondary prevention of signs.

Connect the Dots

Cardiovascular disease (CVD) and coronary heart disease (CHD) are chronic disorders associated with progressive accumulation of inflammatory plaques in coronary and cerebral arteries which provoke ischemic thrombosis, cardiac arrhythmia and death. These processes are exacerbated more by ω -6 eicosanoids than ω -3 eicosanoids, both of which are formed from highly unsaturated fatty acid (HUFA) precursors released from tissue phospholipids by activated phospholipase A₂. Higher proportions of ω -6 in tissue HUFA ensures a higher probability of forming potent ω -6 eicosanoids. The ω -3 and ω -6 in HUFA are maintained by competitive interactions of dietary ω -3 and ω -6 acids with tissue enzymes for elongation, desaturation, acyl transfer and acyl hydrolysis. Because ω -3 and ω -6 chemical structures are not synthesized de novo in vertebrates, the proportions of ω -3 and ω -6 acids maintained by tissue enzymes depend on the proportions of ω -3 and ω -6 acids in foods eaten [3]. This is the chain of molecular events that connect primary food choices to mediators of disease consequences. Intermediate in this causally connected chain is the proportion of ω -6 in tissue HUFA [4].

The proportion of ω -6 in tissue HUFA for many diverse groups worldwide associates closely with the CHD death rates per 100,000 population (fig. 1) [5]. The quintile of American men in the MRFIT study with the lowest estimated proportion of ω -6 in HUFA had the lowest death rate. Thus, the degree of imbalance in tissue HUFA helps predict the likely risk of fatal CHD (fig. 1). People with more than half of their HUFA as ω -6 acids have greater risk of death from CHD than those with less than half. The imbalance in tissue HUFA can be predicted from observed imbalances in dietary fats. As a result, successful nutrition advice to correct imbalanced ω -3 and ω -6 fats in the foods eaten will shift the proportion of ω -6 in tissue HUFA [3, 4] as a valid surrogate endpoint in successful primary prevention of CHD. This surrogate endpoint gives each individual a clear indication of personal risk and also an indication of success in personal compliance with well-focused nutrition advice.

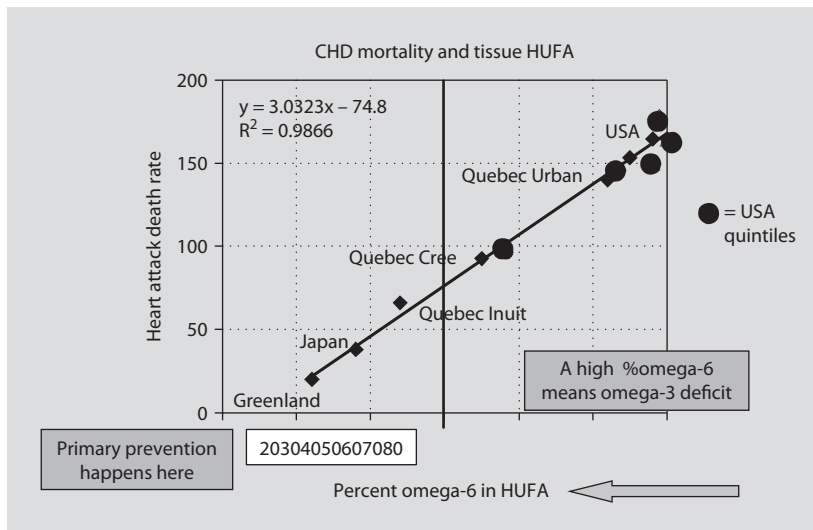


Fig. 1. Strong association of % ω -6 in HUFA with CHD mortality. Heart attack death rates per 100,000 population are linearly related ($R = 0.99$) to the percent of ω -6 in blood HUFA [5]. Four of the USA quintiles are very similar, with only the lowest quintile having appreciably lower death rates.

Describing Balanced and Imbalanced HUFA Proportions

Major fatty acids discussed in this section are indicated by number notations and a letter code for convenience in describing diverse combinations of acids. Eight HUFA accumulate from the competitive metabolic processes that maintain HUFA in tissues. Four are ω -6 acids ($20:3\omega$ -6 = A; $20:4\omega$ -6 = B; $22:4\omega$ -6 = C; $22:5\omega$ -6 = D) maintained by formation from abundant dietary linoleic acid, $18:2\omega$ -6. Three HUFA are ω -3 acids ($20:5\omega$ -3 = F; $22:5\omega$ -3 = G; $22:6\omega$ -3 = H) related to α -linolenic acid ($18:3\omega$ -3 = P), from which they can be formed when competition from ambient linoleic acid ($18:2\omega$ -6 = O) is not too great. One HUFA, ($20:3\omega$ -9 = E), formed from oleic acid ($18:1\omega$ -9 = N), is seldom accumulated when dietary supplies of competing ω -3 or ω -6 fats exceed 2% of daily food energy (2 en%). In the same way, diverse ω -7 HUFA formed from palmitoleic acid ($16:1\omega$ -7 = K) seldom accumulate in humans. This absence occurs because most daily food habits worldwide include more than 2 en% polyunsaturated fatty acids (PUFA), and the HUFA accumulated in human tissues tend to be mostly ω -3 and ω -6 types rather than ω -7 or ω -9 types. For all practical purposes, the total HUFA is the sum of ω -3 and ω -6 HUFA, and the % ω -3 in HUFA equals 100% - % ω -6 in HUFA.

Traditional research laboratory analyses of fatty acid composition report relative amounts of the diverse fatty acids as a percent by weight (wt%) of all the acids analyzed in a sample. The traditional tabular format also arrays abundances of acids in

the sequence they are eluted from the columns. However, many of the up to 30 acids are not used to interpret health status (e.g. 16:0 = J; 18:0 = L; 18:1 ω -9 = N). Alternate formats for reporting HUFA status include presenting just the %EPA in all acids measured (i.e. F), the sum of %EPA + %DHA in all acids measured (F + H), the sum of %EPA + %DPA + %DHA in all acids measured (F + G + H) or as the percent of total acids (equations 1 and 2).

$$\% \omega\text{-3 HUFA in FA} = 100 \times (F + G + H) / (A + B + C + D + E + F + G + H + J + K + L + M + N + O + P) \quad (1)$$

$$\% \omega\text{-6 HUFA in FA} = 100 \times (A + B + C + D) / (A + B + C + D + E + F + G + H + J + K + L + M + N + O + P) \quad (2)$$

In the case of a whole blood sample, assays include fatty acids from erythrocyte phospholipids (with lots of HUFA) as well as plasma triglycerides (with much oleate and linoleate), cholesterol esters (with nearly 50% linoleate) and phospholipids (which mysteriously exclude α -linolenate, 18:3 ω -3). Variable amounts of these diverse lipids and their uninformative acids in different blood samples create 'noise' when evaluating HUFA status. As a result, there is much merit in expressing assay results as proportions of HUFA [6] as in equations 3 and 4 rather than all acids as in equations 1 and 2.

$$\% \omega\text{-3 in HUFA} = 100 \times (F + G + H) / (A + B + C + D + E + F + G + H) \quad (3)$$

$$\% \omega\text{-6 in HUFA} = 100 \times (A + B + C + D) / (A + B + C + D + E + F + G + H) \quad (4)$$

A convenient feature of these biomarkers is that metabolic enzymes are similar in different tissues (and animal species), providing relatively similar competitive interactions among ω -3 and ω -6 acids during elongation, desaturation, acyltransferase and acylhydrolase actions. As a result, the proportions in HUFA are similar in easily sampled tissues, even when the amounts and proportions of ω -3 in the total fatty acids of various lipids differ. For example, plasma fatty acids for Americans had 18% ω -3 and 82% ω -6 in HUFA [7], whereas erythrocytes had 22% ω -3 and 78% ω -6. For Japanese, who have similar enzymes but different average food intakes, plasma had 47% ω -3 and 53% ω -6 in HUFA [8], whereas erythrocytes had 49% ω -3 and 51% ω -6 in HUFA. Other results with rats showed that the % ω -6 in HUFA was similar for liver, plasma and erythrocytes [9].

The similar proportions of HUFA in plasma and erythrocytes make it convenient to measure HUFA in whole blood samples without spending time and effort in centrifuging samples. Because population studies will need assay results from thousands of samples, a 50- μ l 'finger-stick' sample of whole blood seems well-suited to fast-throughput and low-cost assays [10]. To better understand their own personal health options, individuals can compare their personal HUFA profiles with those reported for diverse groups worldwide (fig. 1). That information can be put in the context of published risk for CHD mortality to help individuals make their own interpretations and personal food choices.

Measures of ω -3 HUFA in erythrocyte total fatty acids (equation 1) in Americans had quartile mean values of 3.3, 4.3, 5.0 and 6.5 associated with adjusted odds ratios for risk of primary cardiac arrest of 1.0, 0.5, 0.3 and 0.1 [11]. A recent alternate

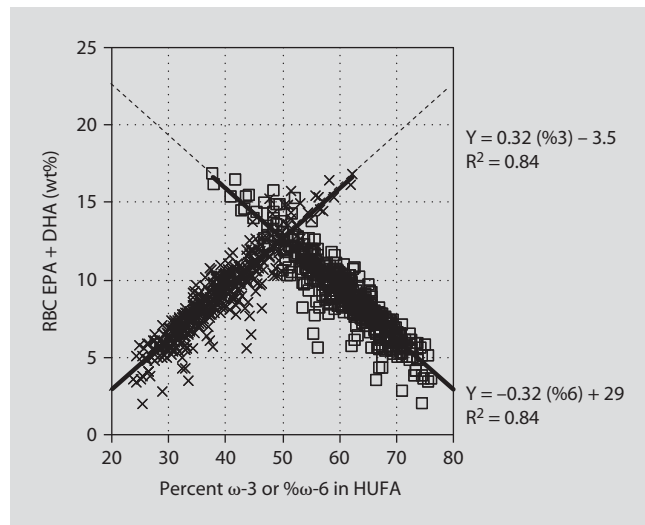


Fig. 2. Comparing three different biomarkers. The proportions of ω -3 in HUFA (crosses) are higher when EPA+DHA are higher, whereas proportions of ω -6 in HUFA (squares) are lower (n = 433).

biomarker omits 22:5 ω -5 from equation 1 [12]. It resembles the biomarker of % ω -3 in HUFA (equation 3). These two biomarkers are correlated strongly for erythrocyte samples from the UK (fig. 2), where foods more closely resembled those in the USA than in Japan. Like in the USA [7], very few people in the UK had more than 50% HUFA as ω -3 HUFA, whereas half the Japanese did [8]. Recent reports show that about half of Japanese may still have erythrocyte values for F + H equal to or greater than 8 wt% [13], whereas only 4% of Americans recently tested did [14], and 65% of Americans had values equal to or lower than 4 wt%. Comparing results in figures 1 and 2 suggests that desirable healthy biomarker values may be above 60% for % ω -3 in blood HUFA and 15 wt% for erythrocyte EPA+DHA (F + H). Few Americans maintain such values.

Competitive Hyperbolic Interactions Maintain Tissue HUFA

Pioneering research by Mohrhauer and Holman documented similar hyperbolic responses of tissue HUFA to dietary supplies of 18:2 ω -6 and 18:3 ω -3 [15] with competitive interactions [16]. Graphic display of the hyperbolic response shows that the midpoint for each 18-carbon dietary precursor in maintaining tissue HUFA is near 0.1 en% [17]. Figure 3 shows that both 18:2 ω -6 and 18:3 ω -3 compete similarly in decreasing accumulation of the ω -9 HUFA, 20:3 ω -9, from its precursor oleate (18:1 ω -9). Such competition also results in a 10-fold impaired accumulation of ω -3 HUFA from 18:3 ω -3 when the dietary supply of 18:2 ω -6 is 8 en%. Neglect of such well-known competitive enzyme dynamics underlies widespread misunderstanding of an observed lack of effect of typical dietary linoleate levels on tissue abundances of



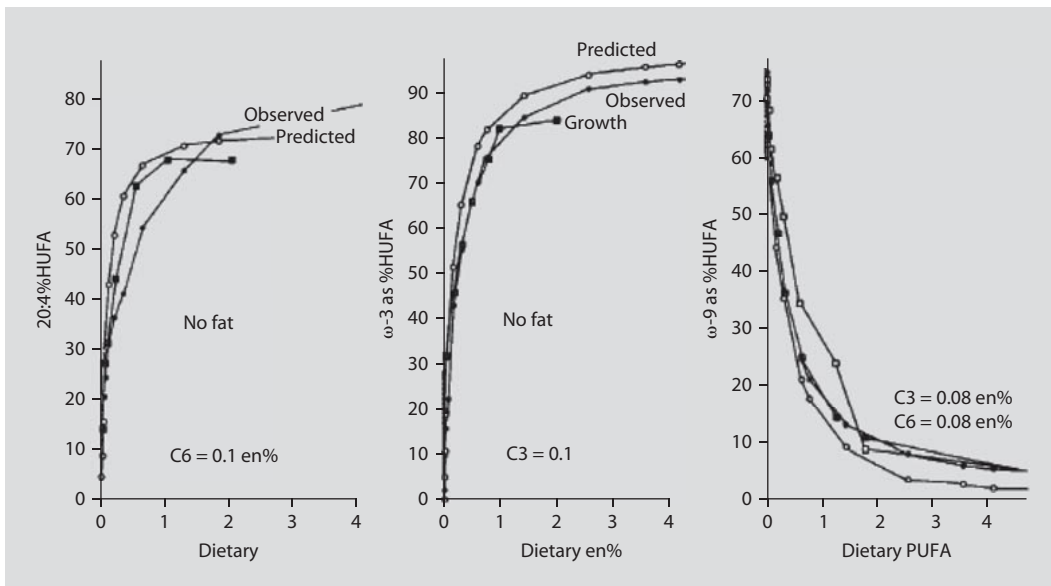


Fig. 3. Observed competitions by dietary precursors in accumulating tissue HUFA. The 1963 results of Mohrhauer and Holman [15] were assessed by Lands [17].

ω -6 HUFA and the observed inefficiency of dietary linolenate in tissue accumulation of ω -3 HUFA. The misunderstanding is particularly harmful in irrational assertions that dietary 18:2 ω -6 is not causal in maintaining tissue levels of the ω -6 HUFA.

Studies with rats [9] confirmed the general competitive metabolic relationship, setting the results into an empirical hyperbolic equation with fitted constants that quantitatively describe this diet-tissue relationship. The empirical equation and constants also fit results for human subjects in Chicago eating 'typical' USA foods [3]. A recent study of the quantitative competitive interactions in humans [18] reported a higher level of ω -3 HUFA occurred with a lower level of dietary ω -6 linoleate – as predicted by the 45-year-old information from rats [15, 16]. Few investigators examine the limits of this competitive relationship. Most research studies consistently feed much more 18:2 ω -6 than 18:3 ω -3 and thereby continue the misunderstandings about an apparent 'weakness' of 18:3 ω -3 in maintaining tissue HUFA and about actions of 18:2 ω -6 in maintaining tissue ω -6 HUFA.

To describe the competitive interactions that maintain lower proportions of ω -6 in tissue HUFA when appreciable amounts of dietary ω -3 HUFA are included, we modified the empirical equation [9] to fit limited data available for rats, mice and humans [3]. The fitted constants allowed close estimates of the amount of supplement taken by patients in Chicago [3]. When two data sets of people eating diverse amounts of ω -3 HUFA became available in 2002, three of the constants were adjusted to fit all data available for a wide range of voluntary dietary PUFA intakes [19]. Figure 4 shows that

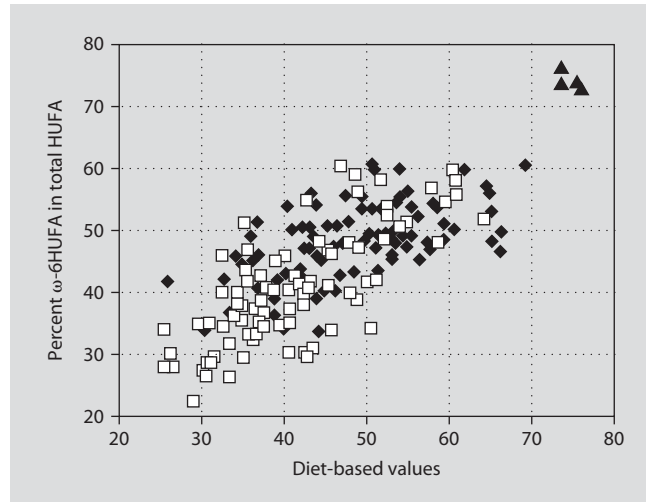


Fig. 4. Agreement of predicted and observed proportions of ω -6 in HUFA. The % ω -6 in HUFA values from USA [3] are in triangles, Japanese rural 57-year-olds [20] in squares, and Japanese urban dietitians [21] in diamonds. Figure reprinted from Lands [22].

the empirical equation makes estimates of likely proportion of ω -6 in blood HUFA that agree well with those measured by gas chromatography. We now have empirical tools to make quantitative estimates of how dietary supplies of ω -3 and ω -6 acids predict the % ω -6 in tissue HUFA and how the % ω -6 in tissue HUFA predicts the risk of cardiovascular disorders.

Dietary Reference Intakes

The Food and Nutrition Board of the Institute of Medicine revised USA nutrient and energy standards to replace older Recommended Dietary Allowance (RDA) with newer Dietary Reference Intakes [23]. An Estimated Average Requirement (EAR) is the nutrient intake estimated to meet the requirement defined by a specified indicator of adequacy in 50% of an age- and gender-specific group. At this level of intake, the remaining 50% of the specified group would not have its needs met. An RDA is the dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals in a particular life stage and gender group. A Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all of the individuals in the general population. As intake increases above the UL, the risk of adverse effects increases.

With regard to an EAR for linoleic acid, unwanted dermal signs were present in 100% infants receiving linoleate at 0.04% of food energy (0.04 en%), but in only 40% of infants receiving linoleate at 0.07 en% and in none receiving 1.3 en% [24]. Thus, the EAR for linoleate may be near 0.06 en%. With regard to an RDA for ω -6 acids, thousands of healthy infants were raised with diets containing ω -6 at 0.4–0.9 en%,



and calculation showed linoleate requirement for 97–98% of infants (i.e. RDA) is likely less than 0.5 en% [25]. Quintiles of dietary intake of linoleate in the USA (2.9, 4.4, 5.5, 6.9, 10.3 en%) are far above the likely RDA [26].

Results in figure 1 indicate a higher likelihood of harm for people with diets that maintain the % ω -6 in HUFA above 50%. In contrast, people who traditionally choose foods that maintain values below 50% are unknowingly practicing primary prevention of CHD. Consumption of ω -3 and ω -6 fats differs greatly for different groups worldwide (column A in table 1), and the % ω -6 in HUFA differs accordingly. Hibbeln et al. [27] estimated that a healthy value of 60% ω -3 in HUFA (40% ω -6 in HUFA) may prevent 97% of the worldwide pathology attributable to an ω -3 HUFA deficit. The authors estimated how much dietary ω -3 HUFA is recommended to maintain a healthy value of 40% ω -6 in HUFA when the other ambient fatty acids remain unchanged (column B in table 1). Alternatively, one could estimate how much dietary ω -6 linoleate is recommended to maintain a healthy value of 40% ω -6 in HUFA when the other ambient fatty acids remain unchanged (column C in table 1). These estimates illustrate the competitive metabolism among essential fatty acids that must be included in making estimates of desirable intakes of nutrients that have opposing effects. Partial decreases in ambient ω -6 linoleate intake permit smaller additions of ω -3 HUFA to achieve the desired healthy biomarker value (column D in table 1). Similar logic was used many years ago [28] in recommending adequate intakes that avoid harmful interdependent effects.

First ... Kill All the Lawyers (Shakespeare, *King Henry VI*, Act 4, Scene 2)

The American public loses annually about USD 400 billion to CVD, which a premier health agency, Centers for Disease Control and Prevention (CDC), regards as preventable [29]. CDC reports heart attacks at 1.2 million annually, and 1 in 3 Americans will die with some form of CVD. Nevertheless, health care agencies continue to focus on treatment of associated signs and risk factors without preventing the primary causal factors [4]. Some organizations may be concerned that effective primary prevention will cut the need for treatments and decrease the flow of funds to clinicians, hospitals and pharmaceutical manufacturers and marketers. Changing the status quo would be a revolutionary reform that puts the interests of citizens and their families above those of the many treatment-oriented corporations that turn their profits into widespread marketing messages and reinforce public focus on treating disease rather than preventing it.

Few corporations are motivated to slow the flow of funds for treatments while the public is frustrated by continually increasing costs for health. Nevertheless, figure 1 and table 1 illustrate how diverse populations worldwide unknowingly practice primary prevention with their traditional food choices. No prescriptions need be written for people to eat foods that give them lower % ω -6 in tissue HUFA and lower ω -6-

Table 1. Desirable nutrient intakes to meet healthy goals

	A					B		C		D		
	Ambient intakes					Est. RDA ω -3H		Est. UL ω -6LA		Blend both ideas		
	1995 Consumption of EFA					fix ω -3 (HUFA)		fix ω -6 (LA)		fix ω -3HUFA and 6LA		
	en% short 3	en% short 6	en% long 3	en% long 6	Est. %6 in H avg	en% long 3	Est. %6 in H avg	en% short 6	Est. %6 in H avg	en% long 3	en% short 6	Est. %6 in H avg
Data from Hibbeln et al. [27]												
Philippines	0.08	0.80	0.26	0.06	34	0.17	40	1.11	40	0.17	0.80	40
Iceland	0.33	2.48	0.44	0.10	50	0.78	40	1.40	40	0.42	1.40	40
Japan	0.78	4.28	0.37	0.10	62	1.30	40	1.40	40	0.40	1.40	40
Denmark	0.33	2.23	0.14	0.09	64	0.66	40	0.63	40	0.40	1.40	40
UK	0.77	3.91	0.10	0.07	70	0.96	40	0.77	40	0.35	1.60	40
Ireland	0.42	3.57	0.09	0.06	71	0.85	40	0.65	40	0.35	1.60	40
Colombia	0.24	3.21	0.05	0.04	73	0.70	40	0.49	40	0.32	1.60	40
Australia	0.49	4.71	0.11	0.07	74	1.20	40	0.70	40	0.32	1.40	40
Italy	0.51	5.40	0.10	0.06	75	1.35	40	0.70	40	0.28	1.40	40
Germany	0.62	5.57	0.08	0.06	76	1.35	40	0.70	40	0.30	1.50	40
Netherlands	0.28	4.23	0.09	0.08	77	1.20	40	0.50	40	0.38	1.40	40
Israel	0.67	7.79	0.12	0.07	79	1.95	40	0.77	40	0.30	1.40	40
USA	1.06	8.91	0.10	0.08	80	2.27	40	0.80	40	0.28	1.40	40
Data from http://efaeducation.nih.gov/sig/diabalance.html												
USA	0.85	6.82	0.03	0.08	82	1.80	40	0.51	40	0.30	1.40	40
Mediterr.	0.50	2.30	0.09	0.08	66	0.60	40	0.59	40	0.32	1.30	40
Japan	0.76	5.04	0.54	0.08	57	1.34	40	2.10	40	0.33	1.40	40

Ambient intakes of polyunsaturated fatty acids differ in different countries (column A), producing different estimated % ω -6 in HUFA. Altering intakes of ω -3 HUFA to give 40% ω -6 in HUFA needs additional amounts from 0.5 to 2 en% (column B). Alternatively, lowering LA (18:2 ω -6) intake by -8 en% can also meet that goal (column C). Column D shows that adjusting both types of nutrient can also meet that goal with less change needed for both nutrients. EFA = Essential fatty acids.

mediated tissue responses [4] that are associated with the severity of atherosclerosis, heart attacks, psychiatric disorders, immune-inflammatory disorders, cancer progression and length of stay in hospitals.

Limited accountability for efficacy of interventions has allowed invalid surrogates and ineffective treatments to substitute for effective prevention of CVD [4]. The unfortunate history of the 1984 Cholesterol Consensus Conference (reviewed in detail elsewhere [4]) led to FDA approval of a cholesterol-lowering therapy without clinical trial evidence demonstrating efficacy. The conference had been convened because of doubts whether the association between CHD and cholesterol had sufficient evidence

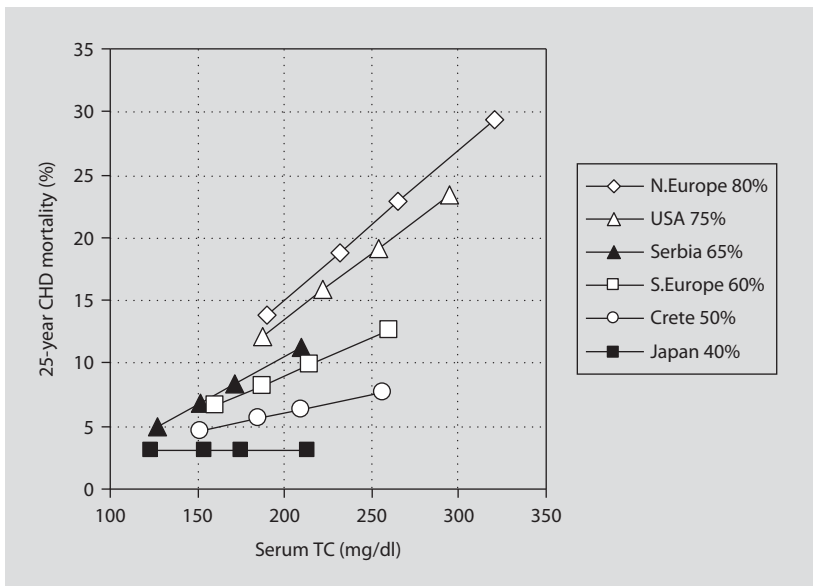


Fig. 5. Risk assessed by blood cholesterol levels depends on tissue HUFA proportions. The dietary factors that elevate blood cholesterol levels may not have fatal outcomes when ω -3 HUFA exceeds ω -6 HUFA. Figure based on results in Verschuren [31] as discussed in Lands [4].

to prove a cause-and-effect relationship with CVD and death. The 14 panel members appointed by the Office of Medical Applications of Research listened to presentations from researchers who were testing new drug candidates (statins). Panel members recognized a causal role for imbalanced food energy and urged caloric restriction and weight loss, stating that “even when use of drugs seems appropriate, it is important to stress that maximal diet therapy should be continued”. Unfortunately, subsequent public information programs aggressively focused on cholesterol-lowering drugs and diverted attention from effective preventive management of food energy. Since then, two decades of poor attention to diet priorities have fostered widespread use of statins and an obesity epidemic while neglecting the primary imbalance of ω -3 and ω -6 fats that causes CVD and death [4].

Much evidence indicates that postprandial oxidant stress following big meals is made worse when ω -6 HUFA exceed ω -3 HUFA [4, 22, 30]. In fact, figure 5 (based on data [31] summarized in [4]) shows that dietary factors which elevate blood cholesterol levels may not have fatal outcomes when ω -3 HUFA exceeds ω -6 HUFA. This effect is quite clear in Japan where mortality among men is least with cholesterol levels above 240 mg/dl and greatest with values below 160 mg/dl [32]. The billions of dollars spent for marketers, lawyers and ill-informed biomedical professionals who focus on treating blood cholesterol levels need to be balanced by efforts to prevent primary causes using clear evidence of causal molecular mechanisms [4]. Measuring

an individual's ω -3 status can refocus attention toward a valid surrogate endpoint and restore accountability for effective preventive health care. People have been distracted from knowing their imbalanced HUFA status for far too long. Once informed, individuals can easily choose foods that prevent the imbalance associated with inflammatory, thrombotic and arrhythmic events in CVD plus inflammatory/proliferative disorders including cancer, dementia, arthritis and asthma as well as psychiatric disorders of depression, suicide and aggression.

When measuring blood fatty acids as a surrogate indicator of CHD risk in population studies, several well-established tools must be arranged for optimal cost-effectiveness: sample acquisition, derivatization, analysis, reporting results. Traditionally, research biochemists describe fatty acids in terms of their chain length and number of double bonds with lists of the various acids in order of their elution during chromatographic analysis. Many diverse acids (up to 30) resolved by gas chromatography are traditionally reported with the amount of each acid described as a percent of all acids analyzed. However, many aspects of chemical structure and elution time are distractions when assessing health status. The proportions of ω -3 and ω -6 HUFA have the most impact on such assessments.

Millions of people will need test results, and a high priority is for easily obtained samples that require little time or effort to handle. A 50- μ l 'finger-stick' blood sample spotted on filter paper [10] may best fit that criterion. Perhaps the simplest derivatization process is microwave-induced transesterification of the blood spot to methyl esters [33], which can then be separated in a robotic fast-throughput gas chromatographic analysis [34]. If priority is given to an even more rapid test, high-speed columns can be used [35] or chromatographic conditions can be arranged to elute even more quickly, sacrificing resolution of earlier peaks that are not used in defining the surrogate endpoint value of % ω -6 in HUFA.

Powerful treatment-oriented interests have secured control of the USD 400 billion lost annually to CVD while the public's health insurance payments continue to rise. The financial resources support many professionals (clinicians, epidemiologists, statisticians, lawyers, lobbyists and marketers) who control the information provided to the public and maintain the status quo and its current levels of disease. The factors that allow appointed advisory panels to ignore causal mechanisms and to promote food choices with intakes of 18:2 ω -6 above 2 en% and ω -3 HUFA below 0.2 en% need more critical examination and justification. The public has inadequate tools to monitor the validity and efficacy of information and advice offered from organizations profiting from treatment rather than prevention. Even widespread advice that maintaining an 8% level of F + H in erythrocytes is 'healthy' needs more critical evaluation in the context of primary prevention of human distress. Unfortunately, even health insurance companies (that could be the public's partner in profiting from prevention) fail to promote effective primary prevention that would cut the need for treatment expenses. They support 'wellness' programs that neglect primary causes and 'go along' with treatment-oriented rationales that maintain high costs for health

care. A populist empathy for revolutionary reform like that expressed in *Henry VI* is readily felt by the public. Similar to results from a global positioning system, removing ignorance about an individual's omega-3 status gives that person a clear indication of where they are and what they can do to correct their condition. Developing low-cost high-throughput tests for HUFA in fingertip blood samples will revolutionize preventive health care worldwide.

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