FISH AND HUMAN HEALTH

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I. INTRODUCTION TO AN OPPORTUNITY

Information on the frequency and severity of diseases among various peoples provides a provocative stimulus for the question, "Why are we different from them (or they from us)?". Once the curiosity begins to be expressed, there is an almost endless series of questions that probe into the mechanisms of diseases and the consequences of life-style and nutrition (e.g. Lands,1986). One of the first concepts that we encounter is that some things that are typical---or *"normal"* --- for one group are often not at all typical (or *"normal"*) for another group. A desire to be *"normal"* leads to the question of "Which *"normal"* (typical) condition is truly desirable?" Possibly what we regard as good and desirable is not typical for our group so that what is *"normal"* for our group may not be desirable!! Considering fish as a food provides an opportunity to examine the relationship of atypical diets and typical health conditions.

The possible health benefits of eating fish (and seafood) have led to a fundamental reexamination of what foods are desirable, and the reexamination led to recognizing that some *"normal"* (typical) disease frequencies and nutrition habits may be neither necessary nor desirable. The different types of dietary polyunsaturated fatty acids that are abundant in foods from the farm (n-6 type) and the ocean (n-3 type) are associated with biochemical mechanisms that have a dramatic influence on certain pathological processes. The following brief review notes important biochemical and physiological consequences that follow nutritional choices of polyunsaturated fatty acids. Each nation's preference for its current *"normal"* dietary habit merits a careful, collective reexamination on a world-wide basis. Even though we do not have enough information to make a fully "informed choice" for future diet decisions, we can share information about disease mechanisms that are influenced by choices of dietary polyunsaturated fatty acids.

Interpreting how the polyunsaturated fatty acids of fish can affect pathophysiology requires an awareness of the competitive interactions of the two major classes of dietary polyunsaturated fatty acids: the n-3 type and the n-6 type and the consequences of choosing either of these two types of polyunsaturated fatty acids for the diet. Competitive interactions occur during: 1.-- incorporation into tissue lipids, 2.-- conversion into 20-and 22-carbon highly unsaturated fatty acids (HUFA), 3.--conversion of HUFA into hormone-like cell regulators (called eicosanoids), and 4.--interaction of the hormone-like derivatives with receptors that modify important cell functions.

Important competitive interactions also occur between the fatty acids synthesized endogenously from carbohydrates and amino acids (16:0, 18:0, 16:1n-7, 18:1n-7, 18:1n-9, 20:3n-7, 20:3n-9, 20:4 n-7) and the exogenous n-3/n-6 fatty acids that cannot be synthesized de novo (18:2n-6, 18:3n-6, 18:3n-3, 20:3n-6, 20:4n-6, 20:5n-3, 22:4n-6, 22:5n-6, 22:5n-3, 22:6n-3). When very small amounts of n-3/n-6 fatty acids are eaten, the endogenous fatty acids are predominant in tissues. However, as increasing amounts of n-3 or n-6 fatty acids are added to the diet, all tissues acquire and maintain appreciable levels of these types of exogenous acids. Biomedical researchers are now attempting to weigh the relative importance of the competitive interactions among the various endogenous and exogenous fatty acids in influencing human health and disease. After fifty years of research on the essentiality of polyunsaturated fatty acids, two fundamental concepts remain uncertain: 1--"Which acids are essential?" and 2--"How much is needed?".

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II. ESSENTIAL REQUIREMENTS AND THE QUESTION OF EXCESSES

A dietary requirement for polyunsaturated fatty acid to support typical growth of young rats (Burr and Burr 1930) was met by either n-3 or n-6 fatty acids, but the prevention of skin abnormalities was achieved only with the n-6 acids (Hume et al 1938; Burr et al.1940). Subsequent studies confirmed the ability of n-3 acids to support the growth, development and gestation of rats (Leat and Northrup 1981), but the inability of n-3 acids to support all of the physiological functions that are supported by the n-6 acids led to excluding the n-3 acids from the "essential fatty acid" category and led to the claim that only the n-6 acids should be regarded as essential (Holman 1960). Recent research emphasizing the probable importance of n-3 acids in retinal (Neuringer et al. 1986) and cerebral (Yamamoto et al. 1987) function is leading increasing numbers of scientists to once again apply the term "essential" to the n-3 type of fatty acids. It seems certain that the n-3 acids play very important roles in membrane assembly and function irrespective of whether or not they are exclusively required for those roles. A recent summary (Lands 1989) suggested that the n-3 acids may provide benefits by providing sufficient 22-carbon acids needed for rapid synthesis of membrane phosphatidyl ethanolamine, whereas the n-6 acids may provide sufficient eicosanoid activity for rapid and vigorous physiological responses. The concept of essentiality is useful in evaluating marginal supplies bordering insufficient (deficiency) and sufficient states, but it is not useful in evaluating the issue of overabundance. If we can regard both acids as important for maintaining a balanced physiology, we may stop searching for a unique feature and concentrate on determining how to maintain the most desirable n-3/n-6 balance.

As for the amount of n-3 and n-6 acids needed in the diet, many careful studies showed no significant physiological inadequacy when diets contained about 0.3 percent of the daily calories (0.3 en%) as 18:2n-6 (e.g. Mohrhauer 1963a, 1963b). Nevertheless, many investigators regard 2 en% 18:2n-6 to be a desirable "normal" dietary level to prevent physiological deficits, and many studies use this level --or higher. The Food and Nutrition Board of the NAS/NRC (USA) noted in 1958 that 1 or 2 en% of 18:2n-6 "should be adequate" for human infants, but a careful quantitative study of 428 infants (Hansen et al. 1963) showed that as little as 0.07 en% 18:2n-6 permitted only about one-half of the pathophysiological signs seen with 0.04 en% 18:2n-6. This finding suggests that the midpoint in the requirement for humans may be similar to that for rats (ca.0.1 en%). Unfortunately, the next higher diet in the study contained 1.3 en% 18:2n-6, and infants receiving it showed no significant physiological deficits. Recalculation and reappraisal of the human studies led Cuthbertson (1976) to estimate that 0.5en% 18:2n-6 would prevent EFA-deficiency symptoms in infants. This level is below that found in most foods, and most humans have 15 to 25% adipose tissue that contains appreciable 18:2n-6 (10-15% by weight). Thus, a 50kg woman or a 70kg man may carry more than 1 kg of 18:2n-6 in reserve fat (50kgx25%x10% and 70x15%x10%, respectively). The combined supply from diet and tissue makes it very improbable that a physiological deficiency of n-6 fatty acids could develop in a typical adult.

III. MECHANISM OF ACTION

Translating the overall complex phenomenon of "essentiality" into discrete physiological and biochemical processes has proceeded slowly, and it remains an exciting area for new research initiatives. One important way in which essential fatty acids influence a wide range of biological events is in forming eicosanoids (prostaglandins and leukotrienes) that participate in the release of hormones by the hypothalamo-pituitary network (Ojeda et al. 1979, 1981). The participation includes: stimulating release of growth hormone releasing factor from the hypothalamus and thus promoting growth hormone release from the pituitary; enhancing the release of prolactin by increasing the prolactin releasing factor and decreasing the prolactin inhibiting factor from the hypothalamus; stimulating the release of luteinizing hormone-releasing factor from the hypothalamus (Hulting et al. 1985; Ottlecz and McCann 1988; Saadi et al. 1990) and thereby stimulating release of gonadotropins from the pituitary. Eicosanoid action probably explains how a restoration of normal weights of testis, prostate and seminal vesicles in animals deficient in essential fatty acids was achieved in 1951(Greenberg and Ershoff 1951) by administration of either oral linoleate (18:2n-6) or injected gonadotropin. The importance of eicosanoids in regulating hypothalamic functions and the influence of the hypothalamo-pituitary system on complex behaviour such as hunger, sex and aggression make

it imperative that we examine carefully the levels of n-3/n-6 acids in diet and tissue which provide desired levels of physiological action.

The "normal" condition of the enzymes which convert cellular HUFA to eicosanoids appears to be suppressed. However, rapid intermittent bursts of synthesis have been described (e.g., Reddi et al. 1990) since the recognition of this phenomenon decades ago by Granstrom and also McCracken. The rapid bursts of synthesis are accompanied by rapid degradation, and they provide only a very brief pulse of active eicosanoid that occupies the cellular receptor, effecting a transient regulatory control. During the transition from suppressed to active states, the capacity for synthesizing n-6 eicosanoids reflects the availability of substrate, 20:4n-6, and competitor, 20:5n-3. The n-3 acid behaves as a partial agonist, diminishing both the formation (Lands et al. 1973) and function of n-6 eicosanoids. In the absence of 20:5n-3, the 20:4n-6 can more easily form active eicosanoids. Apparently, Nature seeks a balance between mechanisms that prevent eicosanoid action and mechanisms that provide explosively rapid bursts of eicosanoids. However, there is no constant level of n-6 eicosanoid to regard as *"normal"* . Thus we need to estimate the desirability of different ***intensities*** of response.

Rather than a deficiency of n-6 fatty acids and eicosanoids, overly intense action of n-6 eicosanoids may be a greater concern. Overaction of n-6 eicosanoids is associated with chronic pathology in many adults (atherosclerosis, thrombosis, vasospasm, arrhythmia, hypertension, arthritis, asthma, immune-inflammatory dysfunctions and some metastatic processes; see Lands 1986). Thus, many typical diseases have n-6 HUFA functioning in an amplifying manner to make the process more severe, and many successful therapeutic tactics diminish the production and function of n-6 eicosanoids. Although stimulation of synthesis is most likely due to factors separate from the dietary supply of n-6 acids, high tissue levels of n-6 HUFA facilitate the synthesis and function of n-6 eicosanoids, whereas tissue n-3 HUFA can decrease that tendency.

IV. COMMON DIET-RELATED DISEASES

In 1988, the Surgeon General of the USA issued a survey that noted that diet played a part in 68% of the total deaths in the USA in 1987. The list included heart disease, myocardial infarction, and cancers of the breast, colon, pancreas and prostate. Biomedical researchers are developing important insights on the degree to which the n-3/n-6 polyunsaturated fatty acids can influence the mechanisms of each of these diseases (Lands 1986).

Coronary heart disease : A study of 6250 American men aged 35 to 57 years (Multiple Risk Factor Intervention Trial; MRFIT) showed that the mean daily intake (180mg) of n-3 20- and 22-carbon highly unsaturated fatty acids (HUFA) was similar to that of the n-6 20-and 22-carbon HUFA (220mg) (Dolecek and Grandits 1990). However, the skewed pattern of intake for this group included many individuals having almost no n-3HUFA in their diets (i.e., no fish), whereas individuals in the upper quintile ingested about 660mg per day. Mortality from cardiovascular disease and coronary heart disease was 40% lower for this latter group (P-values near 0.01).

Mortality from ischaemic heart disease has traditionally also been lower in Japan than in the USA (e.g., in 1985 it was 41 vs 193 per 100000 for Americans; Lands et al.1990a), and the intake of n-3 HUFA in Japan is higher (1500 vs. 100mg/day). Thus international results support the intranational results in suggesting diminished pathology when n-3HUFA are included in the diet. As eicosanoid-related mechanisms for thrombosis (e.g., Lands et al. 1985) and arrhythmias (e.g.,Lockette et al. 1982; Reibel et al. 1988; McLennan and Charnock 1988) become better known, the differences in disease frequencies between the two populations is being increasingly attributed to the different dietary patterns for the amounts and types of fatty acids. A protective action for dietary n-3 acids in diminishing hypertension has also been indicated (Schoene and Fiore 1981; Berry and Hirsch 1986; Codde et al. 1987). Although much public attention remains focussed upon the role of cholesterol-containing lipoproteins in plasma in amplifying atherogenic processes, the actions of the hormone-like derivatives (n-6 eicosanoids) in promoting thrombogenesis and local inflammatory events must also be included in evaluating the overall atherogenic event. Eicosanoid derivatives play significant roles also in immune-inflammatory processes linked to arthritis and asthma (e.g., Endres et al. 1989;

Cleland et al. 1990; Campbell et al. 1990), which, although not directly fatal, greatly decrease the quality of life for many individuals. Thus, the influence of dietary n-3 and n-6 polyunsaturated fatty acids upon cell-cell interactions may have a greater impact upon human health than does dietary cholesterol.

Cancer : When results of the MRFIT study were stratified using the ratio of n-3/n-6 in the overall diet, individuals in the upper quintile (ca. 0.2) had significantly lower cancer mortality ($P<0.03$) than those in the lower quintiles (ca. 0.1). The ratios noted in the study (0.08 to 0.2) reflect a relatively low intake of n-3 acids and a relatively high intake of n-6 acids in the typical *"normal"* American diet. In contrast, the average dietary n-3/n-6 ratio in Japan ranged from 0.34 to 0.26 during the time that the American study was being conducted (Lands et al. 1990a). Thus the typical *"normal"* Japanese ingested a ratio of n-3/n-6 acids which was greater than that of the upper quintile of Americans. The lower 1985 Japanese rates for mortality (per 100000) from breast cancer (4 vs. 17), colon cancer (9 vs. 18) and respiratory cancer (25 vs. 41) should stimulate further examination of the mechanisms whereby the n-3 dietary fatty acids can antagonize tumour proliferation that may be supported by n-6 acids. As the cellular mechanisms for this antagonism become clear, we can expect to re-examine which *"normal"* dietary pattern is actually desirable for health maintenance.

V. MAKING CHOICES

Excessive contention about the desirable types and amounts of polyunsaturated fatty acids for human nutrition might lead some reactionary individuals to choose simply to eat no polyunsaturated fatty acids at all, rather than choose between them. However, the ubiquity of 18:2n-6 makes that choice difficult to pursue because nearly all foods provide the 0.3 en% 18:2n-6 needed to avoid physiological abnormalities. Only severe pursuit of extremely artificial conditions permits one to create an n-6 deficiency. One consequence of following that choice would be that the cellular lipids would become comprised mostly of fatty acids that are formed by endogenous processes (saturated, n-7 and n-9 acids), making the HUFA fraction become predominantly 20:3n-9 rather than 20:4n-6. The resulting low level of 20:4n-6 in the HUFA would provide a low capacity for synthesizing n-6 eicosanoids and would be expected to cause atypical functions of the hypothalamo-pituitary system. An intriguing,but still unexplained phenomenon with low dietary 18:2 n-6 is a decreased expression of Ia antigen on leukocytes, suppressing tissue rejection processes and permitting heterologous transplantation of kidneys (Schreiner et al. 1988).

Including small increasing amounts of 18:2n-6 in the diet permits the tissues (esp. liver) to make increasing amounts of elongated HUFA (20:3n-6, 20:4n-6, 22:4n-6 and 22:5n-6), providing 20:3n-6 and 20:4n-6 for the synthesis of eicosanoids. Alternatively, including small increasing amounts of 18:3n-3 in the diet leads to increasing amounts of the n-3 HUFA (20:5n-3, 22:5n-3 and 22:6n-3) in tissue lipids. The n-3, n-6, n-7 and n-9 types of fatty acid compete with each other for elongation to HUFA and for esterification of the resultant HUFA into glycerolipids of tissues (Mohrhauer and Holman 1963a, 1963b; Machlin 1962). As dietary levels of n-3 and n-6 fatty acids are increased above 0.5 en%, the corresponding HUFA derivatives in phospholipids do not increase proportionally, but tend to approach a limit (Mohrhauer and Holman 1963a, 1963b; Lands et al. 1990b). The gain in n-3/n-6 HUFA with a corresponding loss of n-7/n-9 HUFA illustrates the competition of the various HUFA for a limited number of esterification sites. These competitive interactions can be described quantitatively in the form of hyperbolic equations (Lands et al. 1990b):

$$\text{n-3 as \%HUFA} = \frac{100}{1 + C_3/\text{en\%3}\ [\ 1+\text{en\%6}/C_6+\text{en\%O}/C_O+\text{en\%3}/K_S]}$$

$$\text{n-6 as \%HUFA} = \frac{100}{1 + C_6/\text{en\%6}\ [\ 1+\text{en\%3}/C_3+\text{en\%O}/C_O+\text{en\%6}/K_S]}$$

$$\text{n-3 as \%HUFA} = \frac{100}{1 + K\ [\ 1+\text{en\%3}/C_3+\text{en\%6}/C_6]}$$

Such equations also fit the *ex vivo* ability of platelets to form the n-6 eicosanoid, thromboxane (Hwang and Carroll 1980, as discussed in Lands 1990a), and the *in vivo* tendency for thrombosis (Hornstra 1982, as discussed in Lands 1990a). Thus the capacity for synthesizing n-6 eicosanoids appeared to be a function of the proportion of 20:3n-6+20:4n-6 in the HUFA of glycerophospholipids. At this time, the equations and their associated constants provide approximate quantitative predictions of the effect of dietary fatty acids upon n-3/n-6 compositions in tissue glycerolipids and on the n-6 eicosanoid synthetic capacity in rats (Lands 1990a). Preliminary data suggest that the equations and constants may be similar for rats and humans so that parallel calculations with the amounts of dietary n-3/n-6 acids may help estimate n-6 eicosanoid synthetic capacity in human tissues. If these approximations can be confirmed, then much of the insight on lipids and eicosanoids which was obtained from studies of rats (Lands et al. 1990b) may be conveniently applied to interpreting human studies.

VI. PATTERNS FOR THE FUTURE

Biomedical research of the past two decades provides ample evidence that many disease processes are associated with excessive actions of n-6 eicosanoids which can be diminished by ingesting dietary n-3 fatty acids. Still remaining is the question of whether or not attempts to diminish one of the pathological processes by increasing the dietary ratios of n-3/n-6 acids might cause an undesired imbalance in another process. A recommendation on dietary n-3/n-6 intakes seems unlikely until we understand how much decrease in n-6 eicosanoid capacity is desirable before undesirable side effects appear and how much n-3 is needed to make a significant decrease in the n-6 eicosanoid synthetic capacity. Our collective ignorance of the physiology of excesses has promoted paralysis, and much more physiologically oriented research is needed.

The hyperbolic relationship of dietary polyunsaturated fatty acids to the relative abundance of n-6 eicosanoid precursors in tissue HUFA provides nutrition researchers with a tool to estimate the possible impact of a particular dietary ratio of n-3/n-6 acids. For example, the standard rat chow has been regarded as a "*normal*" diet by many scientists. However, the absence of any appreciable competition from dietary n-3 fatty acids permits rat tissues to maintain levels of 20:4n-6 in the phospholipid HUFA which are comparable to those obtained with diets rich in corn oil (Lands 1990b). Thus in terms of the ability of tissues to maintain phospholipids that have a high capacity for an unchecked synthesis of n-6 eicosanoids (ca. 80%HUFA as 20:4n-6+20:3n-6), the traditional rat chow is near the extreme end of an n-3/n-6 scale of diets. When such an extreme condition is regarded as the normal or desirable condition, investigators may have difficulty in finding encouragement for evaluating conditions that are dispersed along a range of values. Interestingly, the typical diet in the USA also provides abundant n-6 eicosanoid precursors in plasma phospholipids (ca. 70%HUFA as 20:4n-6+20:3n-6). The occurrence of populations or groups of individuals (such as Japanese or Eskimos) who typically maintain their eicosanoid precursors further "down-scale" (ca.40%HUFA as 20:4n-6+20:3n-6) opens the future to new explorations of which ratio of n-3/n-6 acids constitutes a desirable balance.

The sensitive hyperbolic response of tissues to small amounts of dietary 18:2n-6 in the absence of 18:3n-3 indicates that even a low-fat diet that is rich in corn starch will be near the extreme end of the scale of synthetic potential for n-6 eicosanoids. Only by providing effective competitors of the n-6 HUFA esterification into phospholipids can we expect to decrease the relative proportion of n-6 eicosanoid precursors that are maintained in tissue phospholipids. When soy provides the main food oil, the predicted synthetic capacity (ca. 75%HUFA as 20:4n-6+20:3n-6) is slightly lower than that with corn. Shifting to canola oil moves the predicted n-6 eicosanoid capacity somewhat further downscale (60% of PL-HUFA as 20:4n-6+20:3n-6). Only when the corn and soy are almost wholly replaced with flax does the predicted capacity for synthesis of n-6 eicosanoids reach a level (ca. 20-25% HUFA as 20:4n-6+20:3n-6) comparable to that obtained with high supplements of fish oils. Comparisons of the 18-carbon acid, 18:3n-3, with n-3 HUFA indicated that the dietary HUFA were about 2 to 3 times more effective than dietary 18:3n-3 in providing esterified HUFA in the tissue glycerophospholipids (Hwang and Carroll 1980, as discussed in Lands 1990a). Such a result confirms again the greater impact on tissue HUFA of including fish or fish oils in meals compared to vegetable oils.

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The ways that the compositions of tissue n-3/n-6 fatty acids are translated into eicosanoid functions and thereby into physiological responses to stimuli provide a valuable challenge for us all. One valuable contribution of dietary fish to human health has been as a stimulus to reexamine the unfinished status of research on the physiologic impact of the current typical dietary levels of n-6 acids. This reexamination will open new opportunities to understand the delicate balance between action and inaction that successful systems employ in Nature.

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