The Importance of N-3 Fatty Acids in Health and Disease

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Interest in the n-3 fatty acids began some thirty years ago from the remarkable studies in the Greenland Eskimo by the Danish scientists, Dyerberg and Bang. These Eskimos had a low prevalence of coronary heart disease despite a high fat diet because their fat contained high proportions of n-3 fatty acids. This discovery stimulated a large amount of subsequent research about n-3 fatty acids as indicated by the several thousand papers that have appeared in the literature. There is little doubt that n-3 fatty acids have a decisive importance in human nutrition. They are significant structural components of the phospholipid membranes of tissues throughout the body and are especially rich in the retina, brain, and spermatozoa in which docosahexaenoic acid (22:6 n-3 or DHA) constitutes up to 36.4 percent of total fatty acids (1,2). These are all structures where membrane fluidity is essential for proper functioning. In the retina, n-3 fatty acids are especially important. N-3 fatty acid deficiency has resulted in decreased vision and abnormalities of the electroretinogram.

N-3 fatty acids are essential fatty acids, necessary from conception, throughout pregnancy, in infancy and undoubtedly throughout life. A major question is whether there is need in the human diet for the entire spectrum of n-3 fatty acids from the 18 carbon alpha linolenic acid with three double bonds (18:3 n-3) to the highly polyunsaturated 22:6 n-3 (DHA). Since DHA can be synthesized from 18:3 n-3, is there a need for DRA in infant formulas? Or should DHA be supplied to infant formulas in addition to linolenic acid? DHA is certainly transferred across the placenta to the fetus during pregnancy (3) and it is always present in human milk along with other n-3 fatty acids including linolenic acid. A second question relates to the proper ratio in the diet of the n-6 fatty acids to the n-3 fatty acids. An imbalance in this ratio can accentuate the n-3 fatty acid deficiency state. The n-6/n-3 ratio may have been increased in industrialized societies from the use of vegetable oils rich in the n-6 linoleic acids and from reduced consumption of n-3 rich foods. Since both n-3 and n-6 fatty acids are essential, the ratio of the n-6 fatty acid, arachidonic (20:4) to DHA may be important also.

The second important feature of the n-3 fatty acid family is in their role in the prevention and modulation of certain diseases so common in Western civilization. Rather firm evidence is available for certain diseases and less certain evidence, even speculation, about other disorders. A partial listing of such disorders which is by no means complete is provided in table 1.

TABLE I
DISEASES WHICH N-3 FATTY ACIDS MAY POSSIBLY PREVENT OR AMELIORATE

	Strength of the Evidence
Coronary heart disease and stroke	4+
Essential fatty acid deficiency in infancy (retinal and brain development)	4+
Mild hypertension	1+
Rheumatoid arthritis	1+
Autoimmune disorders (lupus, nephropathy)	3+
Crohn's disease of the bowel	3+
Cancer (breast, colon, prostate, etc.)	2+

There is a grading of the weight of the scientific evidence from 1-4, the highest number indicating the greatest strength of the available evidence as perceived by this reviewer.

Cardiovascular Effects of N-3 Fatty Acids

The strongest evidence about the protective effects of n-3 fatty acids relates to their levels in the diet and in the blood and tissues and the occurrence of coronary heart disease and its many complications. The effects of n-3 fatty acids upon coronary heart disease are based upon hundreds of experiments in animals, humans, tissue culture studies and even clinical trials (4).

While saturated fat and cholesterol in the diet are pathogenic for coronary heart disease, the n-3 fatty acids

from fish are actually protective and by a variety of mechanisms prevent coronary deaths and, in particular, cardiac arrest (5). The unique properties of these fatty acids in coronary heart disease first became apparent in the investigations of the health status of Greenland Eskimos who consumed a very high fat diet from seal, whale and fish and yet had a low attack rate of coronary heart disease (6,7). Further studies clarified this paradox. The kind of fat the Eskimos consumed contained large quantities of n-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These were the very long chained and highly polyunsaturated fatty acids with 20 and 22 carbons and 5 and 6 double bonds, 20:5 (EPA) and 22:6 (DHA) n-3 respectively. EPA and DHA are found in fish, shellfish and sea mammals and are very low in quantity or absent in land animals and plants. EPA and DHA are synthesized by phytoplankton, the plants of the waters and the base of the food chain for marine life. However, the plants of the land also provide a rich source of another n-3 fatty acid, the 18 carbon, alpha linolenic acid (18:3 n-3), from which EPA and DHA may be synthesized and which may in itself have health benefits.

N-3 fatty acids in the diet act to prevent coronary disease by a variety of actions:(4)

TABLE 2
IMPORTANT BIOLOGICAL ACTIONS OF N-3 FATTY ACIDS FROM FISH AND FISH OIL TO PREVENT CARDIOVASCULAR DISEASE

- Prevention of arrhythmias (ventricular tachycardia and ventricular fibrillation)
- Anti-thrombotic activity
- Prostaglandin and leukotriene precursors
- Anti-inflammatory properties
- Inhibition of synthesis of cytokins and mitogens
- Stimulation of endothelial-derived nitric oxide
- Inhibit atherosclerosis
- Hypolipidemic properties: triglyceride, VLDL

EPA and DHA have a strong antiarrythmic action on the heart, as recently reviewed by Kang and Leaf (5). In experimental animals and tissue culture systems, EPA and DHA prevent the development of ventricular tachycardia and fibrillation. If EPA or DHA is given to isolated, contracting myocytes in culture, they will abort the ventricular fibrillation induced by a number of noxious pharmaceutical agents such as ouabain. Even total mortality has been improved in several studies in which the n-3 fatty acid intake was increased. In those men who consumed salmon at least once a week had a 70% less likelihood of cardiac arrest (8). In another study by Burr et.al. overall mortality was decreased by 29% in men with overt cardiovascular disease given n-3 fatty acids from fish or fish oil, probably by the reduction in cardiac arrests (9). In a third study in France coronary deaths, especially sudden deaths, were prevented by a diet high in the n-3 linolenic acid (10).

The most recent study about fish consumption and the risk of sudden cardiac death was from the Physician's Health Study in the US in which 20,551 male physicians participated (11). The consumption of at least 1 fish meal per week was associated with a 52% lower risk of sudden death compared with minimal fish consumption. The total mortality in this sample was also reduced by those who ate fish. There did not appear to be a greater reduction in sudden death in those who ate more than 1 fish meal per week, suggesting a threshold effect. A similar threshold occurred for the intake of n-3 fatty acids. Even a small intake was associated in a reduction in sudden death, from 0.3 to 2.7 g per month. There was not a reduced risk of total myocardial infarction, non-sudden cardiac death, or total cardiovascular mortality. The limitations of this study are that the nutritional history was taken upon entry to the study and then cardiovascular events including sudden death were followed up for eleven years. Clearly fish intake could have varied over this period of time, especially since the study involved physicians who certainly would have been aware of the overall beneficial effects of fish consumption. There is also no indication of fish oil usage which physicians subsequently might well have taken in an effort to prevent coronary disease.

Thrombosis is a major complication of coronary atherosclerosis, which leads to myocardial infarction. The n-3 fatty acids from fish oil have powerful antithrombotic actions. EPA inhibits the synthesis of thromboxane A2 from arachidonic acid in platelets (12). This prostaglandin causes platelet aggregation and vasoconstruction. As a result, fish

oil ingestion by humans increases the bleeding time and decreases the stickiness of the platelets for aggregation to glass beads (13). In addition, the administration of fish oil enhances the production of prostacyclin, a prostaglandin that produces vasodilation and less sticky platelets (12). In an in vivo baboon model, dietary fish oil prevented platelet deposition in a plastic vascular shunt (14). Injury to the intima of the carotid artery of the baboon invariably caused a marked proliferative and inflammatory lesion, greatly thickening the wall. When the animals were fed fish oil, this damage and intimal thickening were completely blocked.

The EPA and DHA contained in fish oil fed to experimental animals actually inhibited development of atherosclerosis. There is evidence in both pigs and monkeys that dietary fish oil prevents atherosclerosis by actions other than through lowering plasma cholesterol concentrations (15,16). These actions may be associated with the inhibition of monocyte migration into the plaque, with less cytokine and interleukin-1 alpha production, and through stimulation of the endothelial production of nitric oxide (17). What was previously known as endothelial-derived relaxing factor (EDRF) has been now identified as nitric oxide and this beneficial substance is enhanced by the n-3 fatty acids in fish oil.

Atherosclerotic plaque formation may also be lessened by the reduction in growth factors after fish-oil consumption, particularly platelet-derived growth factor, which is a potent mitogen for cellular growth (18). Not only is platelet-derived growth factor diminished by fish oil, but even its messenger RNA is reduced. Because atherosclerosis begins with cellular proliferation in response to the influx of cholesterol-rich lipoproteins, the inhibition of this proliferation would greatly reduce the growth of the atherosclerotic plaque.

The pronounced effect of fish oil on hyperlipidernia is especially well documented and is supported by precise dietary studies in a diet rich in salmon oil was fed and contrasted with a vegetable oil diet and a diet high in saturated fat. Fish oil especially lowers plasma cholesterol and triacylglycerol concentrations through inhibition of the synthesis of triacylglycerol and very low-density lipoprotein (VLDL) in the liver (19,20). Apolipoprotein B production is reduced by consumption of fish oil in comparison with vegetable oils such as safflower or olive oil (21). This mechanism of action is further substantiated by cultures of rabbit and rat hepatocytes in which EPA, for example, in contrast to oleic acid, inhibited triglyceride synthesis and stimulated the synthesis of membrane phospholipid (22).

The occasional increase in low-density lipoprotein (LDL) concentrations that occurs after VLDL and triacylglycerol concentrations are greatly lowered by fish oil is similar to the increase in LDL that occurs after the drug gemfibrozil is given. LDL synthesis was reduced and plasma levels lowered by large doses of fish oil (23). In contrast with the n-6 rich vegetable oils that lower high-density lipoprotein (HDL), fish oil does not decrease HDL (19).

Pronounced postprandial lipermia occurs after the absorption of fat in diets with a high fat content. Postprandial lipoproteins are known to be atherogenic. They are also thrombogenic because postprandial lipernia increases activated factor VII, a procoagulant (24). Postprandial lipernia from fatty meals of different fats produced similar activation of factor VII (25). Olive oil, highly touted as a highly beneficial monounsaturated fat led to just as much activated factor VII as four other fats including butter. Pretreatment with fish oil greatly lessens postprandial lipernia (26) and this effect should be considered both antiatherogenic and antithrombotic.

The interaction of dietary saturated fatty acids and fish oil on both thrombotic factors and hyperlipidernia is of interest and was evaluated in healthy men (27). The effect of n-3 fatty acids, principally EPA and DHA, was similar in all diets regardless of variable intakes of saturated fat. With regard to effects upon the plasma lipids and lipoproteins from the high and low saturated fat diets, the presence of n-3 fatty acids significantly lowered the plasma total cholesterol, very low density lipoprotein cholesterol, HDL cholesterol, total triglyceride and very low density lipoprotein triglyceride. Since the low saturated fat diet decreased the total cholesterol and LDL and HDL cholesterol, these results indicated that dietary saturated fats and n-3 fatty acids had independent mechanisms of actions on the plasma lipids and lipoproteins. Optimal plasma lipid resulted when the diet was low in saturated fatty acids and high in n-3 fatty acids. The most favorable outcome on platelet function and platelet vascular interactions was obtained when a low fat diet was supplemented with n-3 fatty acids. A significantly longer bleeding time occurred when n-3 fatty acids were added to a low saturated fat diet compared to when it was added to a diet rich in saturated fats (24). Apparently a diet high in saturated fats may counteract the beneficial effects of n-3 fatty acids on the platelet-vessel well interaction.

Ideally, the diet best designed to produce the optimal action to prevent cardiovascular disease would be low in saturated fatty acids and high in EPA and DHA from fish or fish oil (27). The low- saturated fat diet would lower total cholesterol and LDL and the fish oil would lower triacylglycerol and VLDL and have an antithrombotic action. However, as already emphasized, the most powerful

action of the n-3 fatty acids from fish and fish oil in cardiovascular disease is to prevent ventricular fibrillation and sudden death.

The Essentiality of N-3 Fatty Acids as Components of Membrane Phospholipids in Infancy

There are two critical periods for the acquisition of these essential n-3 fatty acids: during fetal development and after birth until the biochemical development in the brain and retina is completed. As already noted, the n-3 docosahexaenoic acid is an important constituent of the membrane phospholipids of these neural structures, usually occupying the sn-2 position. A typical example is phosphatidyl ethanolamine, especially rich in the brain and retina whose structure is shown in the figure. Note that docosahexaenoic acid (22:6 n-3) occupies the number two position on the glycerol backbone and that stearic acid occupies the number one position in this molecule. Other phospholipids in which docosahexaenoic acid is a prominent feature include phosphatidyl choline or lecithin, phosphatidyl inositol, phosphatidyl serine, cerebrosides and sphingomyelin. There are dozens of different molecular species in the brain and retina as has been denoted in several publications on this subject (28,29).

The specific findings of n-3 fatty acid deficiency are manifested in both the blood and tissue biochemistry (I). Of note is a strikingly low concentration of docosahexaenoic acid, which may fall to as much as one-fifth of the normal amount. In addition, the body attempts to replace the deficient docosahexaenoic acid with another highly polyunsaturated fatty acid of the n-6 series. This is docosapentaenoic acid (22:5 n-6). Thus, the total polyunsaturated fatty acid content of the membranes may be quite similar, even with a deficiency of docosahexaenoic acid because of its replacement with this polyunsaturated n-6 fatty acid. In the rhesus monkey an n-3 deficient diet administered to the pregnant animal and then continued after birth induces profound functional changes such as reduced vision, abnormalities of the electroretinogram, impaired visual evoked potential, polydipsia, more stereotypic behavior and perhaps disturbances of cognition (30,31).

Some of these findings have been replicated in infants fed formulas deficient in n-3 fatty acid (i.e. corn oil - coconut oil formulas). However, in human infants the results have been more variable and obviously the experimental protocols less rigorous because of ethical considerations. Even so in most studies of premature infants there have been visual impairment and abnormal electroretinograms. In full term infants the results have been more ambiguous. Yet a recent study of full term infants comparing a standard infant formula with human milk and to formulas enriched with DHA provided unequivocal evidence of considerable differences in the visual evoked potential (32). In all of the human studies the biochemical evidence in the plasma, red blood cells and occasionally in tissues from autopsied infants has substantiated the n-3 fatty acid deficiency state. The lower concentrations of DHA in the plasma and erythrocytes are mirrored by lower concentrations in the brain and retina (1). Formula fed infants have lower concentrations of DHA in the brain than infants fed human milk (33,34). They also have lower intelligence quotients (35).

During pregnancy the maternal stores of n-3 fatty acids and the dietary intakes of those fatty acids by the pregnant woman are both of importance in insuring that the fetus has adequate amounts of n-3 fatty acids at the time of birth. All of the polyunsaturated fatty acids, including DHA, are transferred across the placenta into fetal blood (3). In addition, EPA and DHA in maternal adipose tissue can be mobilized as free fatty acids bound to albumin and be made available to the developing fetus via placenta transport. Several studies in monkeys have indicated that when the maternal diet is deficient in n-3 fatty acids, the infant at birth is likewise deficient in n-3 fatty acids and has biochemical evidence of this state in that the plasma and red blood cells have a much lower concentration of docosahexaenoic acid (30). In humans a recent study demonstrated that the administration of fish oil or sardines to pregnant women led to higher levels of DHA in both maternal plasma and red blood cells and in the fetal cord blood plasma and red blood cells at the time of birth (36). Once membrane phospholipids have adequate concentrations of docosahexaenoic acid, there is an avid retention of these fatty acids in the brain and the retina, even though the diet may subsequently be deficient. A number of papers in this symposium clearly illustrate the effects of n-3 deficiency in both animals and humans.

A crucial question for the scientific community and regulatory health bodies throughout the world relates to the amount and kinds of n-3 fatty acids, which should be incorporated in infant formulas. It is, of course, completely accepted that infant formulas should contain adequate amounts of n-6 fatty acids. In this context the history of infant formulas is of interest. For many years infants whose mothers could not feed them human milk were given cow's milk diluted with water and reinforced with added sugar (37). These modified cow's milk formulas are currently still used in many parts of the world where poverty or the habits of life prevent the use of commercial infant formulas. The essential fatty acid status of cow's milk is questionable even though the ratio of n-6 linoleic acid to the n-3 linolenic acid

is appropriate and is in the 2 to 1 range. The percent of essential fatty acids in terms of total calories falls far short of WHO recommendations. Modified cow's milk has 2% of n-6 fatty acids and 1% of n-3 fatty acids in terms of percent of total calories. Only linoleic and linolenic acids are found in cow's milk. There are few, if any, detailed studies of the biochemistry and the function of infants fed cow's milk.

As noted in the prominent text by Fornon on infant nutrition, infant formulas have undergone many changes since their genesis (37). A typical corn oil-coconut oil formula has a plethora of the n-6 linoleic acid and very little of the n-3 linolenic acid. Such formulas were still being marketed up to several years ago in a country such as Mexico (3 1). In the USA such formulas were changed in the 1980's and soybean oil which has a very good ratio of linoleic to linolenic acid, seven to one, was introduced. The use of soybean oil has greatly approved the n-3 fatty acid status of currently marketed formulas. The debate now is whether infant formula could be further improved by the addition of the highly polyunsaturated fatty acids of both the n-3 (DHA) and n-6 (arachidonic acid) categories. This potential improvement in infant formulas so as to make them similar in fatty content of human milk is enjoined by several papers in this symposium.

In summary, the n-3 fatty acids have important effects to modulate and prevent human diseases, particularly coronary heart disease. Their effects upon the brain later in life to prevent certain disorders such as Alzheimer's Disease are unknown but are certainly worthy of study. Certainly the evidence is now very strong that the n-3 fatty acids are essential for human development in the fetus and infant and are likely to have a role throughout life. The antiarrythmic effect of n-3 fatty acids is a discovery that has great relevance to the prevention of sudden death from ventricular fibrillation in patients with coronary heart disease. Further clinical trials in this area are definitely indicated.

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