A REVIEW OF THE EFFECTS OF OMEGA-3 MARINE FISH OILS: PANACEA OR PLACEBO ?

John H. Juhl, D. O.

1988

ABSTRACT

Possible applications of dietary supplementation with marine fish oils are suggested by studies showing the reversal or slowing of cardiovascular disease[1,4-8], reductions in hyperlipidemia[9,11], mildly elevated blood pressure[10,11], peripheral vascular disease[8,12], increased insulin sensitivity in Type II diabetics[13-16], and palliative relief in the treatment of acute rheumatoid arthritis[17,18].

At the molecular, cell membrane, organ and systemic vascular levels physiologic changes have been induced and quantified after dietary supplementation with fish oils. Numerous animal studies have shown a salutary effect on various aspects of the atherosclerotic process. In human studies, many individual results are contradictory, but some broad trends have emerged.

Dietary introduction of marine fish oils has an antiinflammatory effect via damping of the arachidonic acid cascade; an antiatherogenic effect via modulation of platelet function and blood lipid levels, and it may have a pro-insulin effect via some secondary mechanism involving membrane receptors and/or membrane protein function.

If large scale double blind placebo controlled clinical studies continue to support the findings of prior studies, marine fish oils may well become the most essential dietary supplement for adult populations in industrial countries.

In the last 20 years over 600 papers have been published on subjects related to cold water marine fish oils. Over 60 of these were related to heart disease. Recent preliminary results of the Physicians Health Study[2] investigating the effects of alternate day low dose aspirin therapy on cardiovascular disease provide the best support to date of the beneficial effects of intervention in the atherosclerotic process at the level of platelet function and the prostaglandin pathways.

Possible applications of dietary supplementation with marine fish oils are suggested by studies showing the reversal or slowing of cardiovascular disease [1,4-8], reductions in hyperlipidemia [9,11], mildly elevated blood pressure[10,11], peripheral vascular disease[8,12], increased insulin sensitivity in Type II diabetics[13-16], and palliative relief in the treatment of acute rheumatoid arthritis[17,18].

This paper will review the current understanding of the basic physiological mechanisms involved, as well as some of the epidemiological and clinical studies to date. For those whose interest is kindled, the 3/3/88 NEJM article on the cardiovascular effects of n-3 fatty acids by Leaf and Weber[1] provides an extensive bibliography.

The retail fish industry has grown within the period of a few years from three to 40 million dollars annual sales. They are not classified as drugs by the F.D.A., although they appear to have a number of pharmacological properties. While our intrinsic scientific skepticism should put us on guard against the various recent "snake oils" put on the market such as vitamin B-16 or laetril, at the least we should be as knowledgable about the subject as our patients who will be asking advice on the subject.

What exactly are marine fish oils ? Simplistically, they can be thought of as a biological antifreeze. At the molecular level they can be thought of as fatty acids having longer chains with more double bonds than the usual fatty acids that act as tails for the phospholipids that are the major building blocks of the bilayered lipid membranes that encase the fluid compartments of the body.

The proper names for the marine fatty acids are eicosapentaenoic and docosahexaenoic acid, the name indicating the carbon chain length and the number of double bonds. Hence in Figure 1

EicosaPENTaenoic C20:5 n-3, and

DocosaHEXaenoic C22:6 n-3 acid,

where for example the C20 refers to the carbon chain length, and :5 refers to the number of carbon-carbon "unsaturated" double bonds. What unites these two fatty acids as a family, is the Omega or n-3 designation, which indicates the number of the closest carbon-carbon double bond to the methyl end of the chain. Thus, the n-6 and n-9 fatty acids have a final double bond at the 6th or 9th carbon from the end of the chain, and they are derived from vegetable and animal fats. The n-3 family has a double bond at just the 3rd carbon from the methyl end of the chain, and includes the marine fish oils as well as the essential fatty acid alpha-linolenic acid, which is generated soley by plant chloroplasts.

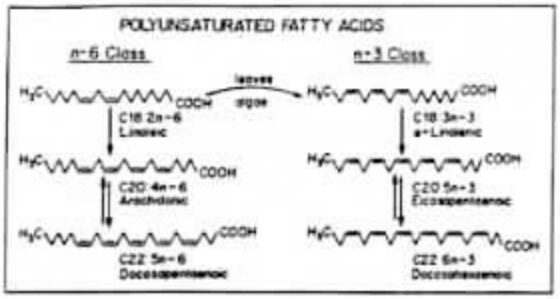


Figure 1. Relation of Important Polyunsaturated Fatty Acids of the n-6 and n-3 Classes.

The transformations depicted by the arrows incorporate two or more reaction steps. The chemical and spatial formulas of the fatty acids are shown. For example, in C18:2n-6, the chemical formula for linoleic acid, C18 indicates the number of carbon atoms and 2 the number of unsaturated carbon–carbon double bonds, the position of which is shown in the adjacent spatial formula. n-6 denotes both the number of carbon atoms from the methyl end of the molecule to the first double bond and the class of fatty acid. The arching arrow indicates that only in leaves and algae is n-6 linoleic acid desaturated to form n-3 alpha-linolenic acid, the progenitor of the n-3 class of fatty acids.

NEJM,vol.318:#9,p.550,'88

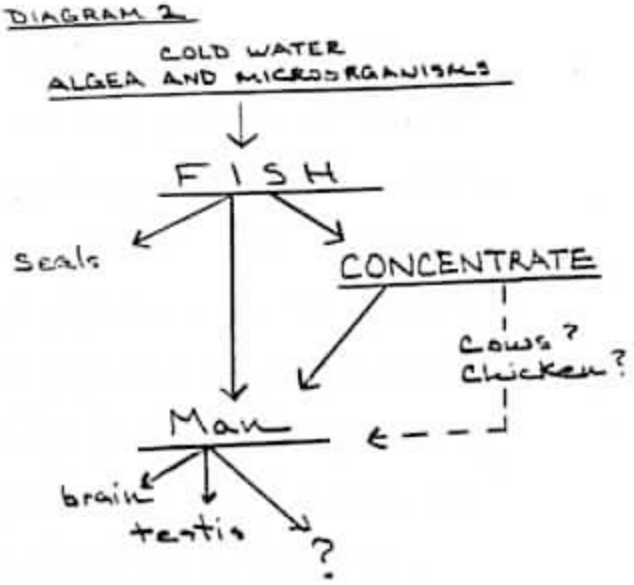
Where do the marine fish oils come from ? Their dietary impact comes primarily from cold water marine fish and a representative list can be found in Table 1 . While mackerel is the foremost representative of the "fatty" fish, many unlisted "lean" fish have lesser amounts; but the source appears to be farther down the food chain. Cold water algea and phytoplankton produce

Table 1. Cholesterol and Calories in Fish and Dietary Supplements Supplying 1 g of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA).*

Fish or Supplement	Fat†	EPA + DHA†	Cholesterol†	Calories†	Amount To Supply ~1 g of EPA + DHA	Cholesterol	Calories
	g	g	mg	no.	g	mg	no.
Cod	0.7	0.2	37	Steamed 82 Fried 204	500	185	410 1020
Flounder	1.0	0.2	46	Steamed 53 Fried 214	500	230	265 1070
Salmon	6.6	1.0	74	Steamed 199	100	74	199
Trout	3.4	0.5	57	Steamed 131	200	114	262
Crab	1.3	0.4	78	Boiled 127	250	195	317
Lobster	0.9	0.2	95	Boiled 119	500	475	595
Shrimp	1.3	0.2	128	Boiled 114	500	640	570
MaxEPA fish-oil concentrate	100	30	450	930	3	14	30
Cod-liver oil	100	22	500	930	5	25	46

*Based on data from the U.S. Department of Agriculture[1] and McCance and Widdowson.[2]
†All values are per 100-g portion. NEJM, vol. 316:#10, p. 626, '87

DIAGRAM 2



these fatty acids which are concentrated by fish that are the food source for sea mammals, other fish, and man. There does seem to be some endogenous production in man, since small amounts are found to be conserved in brain tissue and testis.

Platelets and erythrocytes because of their short half life are more quickly affected by dietary increases of n-3 fatty acids than other tissues.[19] Docosahexaenoic acid (DHA) is converted to, and thus acts as a storage form for eicosapentaenoic acid (EPA)[1]. Both inhibit platelet aggregation[1,8]. EPA has been shown to reduce whole blood viscosity and increase red blood cell deformability[8] as well as increasing template bleeding time[20,23]. Both heart and skeletal muscle appear to be responsive to dietary changes in polyunsaturated n-3 fatty acids[3].

Table 2 includes some of the commercially available marine fish oil preparations.

Table 2. Vitamin A Content, Unit Package Size and Price, and Recommended Daily Intake for Several Commercial Fish-Oil Preparations.*

Brand Name	Unit Package	Recommended Daily Intake	Omega-3 Fatty Acid/ Capsule		RDA of Vitamin A/Capsule	Price
			EPA	DHA		
	no. of capsules		mg		%	$
GNC Mega-EPA-1000	90	3–6	180	120	1	9.99
Royal Oak epa-Plus	100	3–6	180	120	NG	5.50
Solgar Max EPA	50	2	180	120	2	7.95
Dale Alexander Norwegian cod-liver oil	100	1–6	377	38	50	3.75
Omegacaps	240	2	700	300	n.g.	54.00

*EPA denotes eicosapentaenoic acid (20:5ω3), DHA docosahexaenoic acid (22:6ω3), RDA recommended daily allowance, and NG not given.
†Value is the average of the range given.
adopted from NEJM, vol. 316:#10, p. 626, '87

Historical Dietary Injunctions

Prior to the 20th century atherosclerosis, like gout, was primarily a disease of the wealthy. Fasting and abstinence from food products on the other hand has a long history. In the Jewish tradition fasting was practiced as early as the destruction of the first temple, and was equated with bereavement and national mourning. Dietary restrictions separated meat meals from dairy meals increasing the reliance on grains and fruits. The ingestion of pork or shellfish products are prohibited. In the Moslem tradition the prohibition on the eating of pork was retained, and the month of Ramadan is observed with a fast during daylight hours. In the Hindu religion the cow is sacred and is not eaten.

While Jesus apparently did not observe all the Jewish fast laws, the Church early on reinstituted fasts on Wednesdays and Fridays, and by the time of Athenasius in 337 A.D., the Eastern and Western Churches uniformly observed the current 40 day period of Lent[35]. Catholics until very recent times would abstain from meat on Fridays, often substituting fish for protein.

In English literature as early as 1653, fish consumption was touted as a prescription for a long and healthy life[21].

Epidemiology

Numerous sources have documented the lower incidence of coronary artery disease (CAD) in populations whose diet includes a large component of fish. Low death rates from CAD are found in Japan where fish consumption averages 100 gm/day. The lowest rates are found in Okinawa where fish sonsumption is double that national average. Second generation Japanese-americans however, loose their epidemiological advantage with respect to CAD[4].

A seminal retrospective study published in 1980 looked at a relatively stable population of 1800 Greenland eskimos over a period of 20 years. They found an increased incidence of apoplexy (sic.) and epilepsy, but significantly lower incidences of acute myocardial infarction, diabetes, asthma and psoriasis in comparison to a control danish population. Cancer rates were similar [22].

The study that generated the most interest is the Zutphen Study that compared the incidence of CAD and fish consumption in 800 Netherlander men over a period of 20 years. Consumption of as little as 30 gm/day of fish correlated inversely with heart disease for the 20 year period. This correlation was significant over the entire range from high to low fish consumption. Thus, consumption of as little as 30 gm/day of fish lowered the risk of heart disease 2.5 fold. Only age, fish consumption and dietary cholesterol significantly related to CAD mortality. They further concluded that platelet aggregation is reduced and bleeding time increased by fatty fish intakeof greater than 100 gm/day[4].

More recent papers have suggested that Eskimos are genetically predisposed to low incidence of CAD by virtue of a selective lipid enzyme defect that diminishes the production of endogenous arachidonic acid[23]. These and other epidemiological studies were like bait to numerous basic research groups interested in interventions that would effect the endemic level of heart disease in North American and European populations, but the hook was the overlap with the quickly evolving field of prostaglandins.

The Arachidonic Acid Cascade

Some 80 years after the introduction of commercial aspirin therapy, a coherent mechanism of action was beginning to emerge, and each year discoveries are being published clarifying individual components of the cellular level information and amplification system of the prostaglandins.

To understand the effect of the introduction of n-3 fatty acids on the prostaglandin pathways we need to review the arachidonic acid cascade and its effect on vascular tissue. In Diagram 4 we can see that the effect of introducing EPA as substrate in place of arachidonic acid (AA) is to produce a general damping of the AA cascade, and a shift from inflammatory, aggregatory and atherogenic products to more anti-inflammatory, anti-aggregatory, vasodilatory vascular products. Thus, the EPA generated metabolites leukotriene B5 (LTB5) and Thromboxane A3 (TXA3) are considerably less active than their arachidonic acid generated counterparts, while Prostaglandin I3 (PGI3) has similar vasodilatory activity in comparison with the arachidonic acid product PGI2 (prostacyclin).

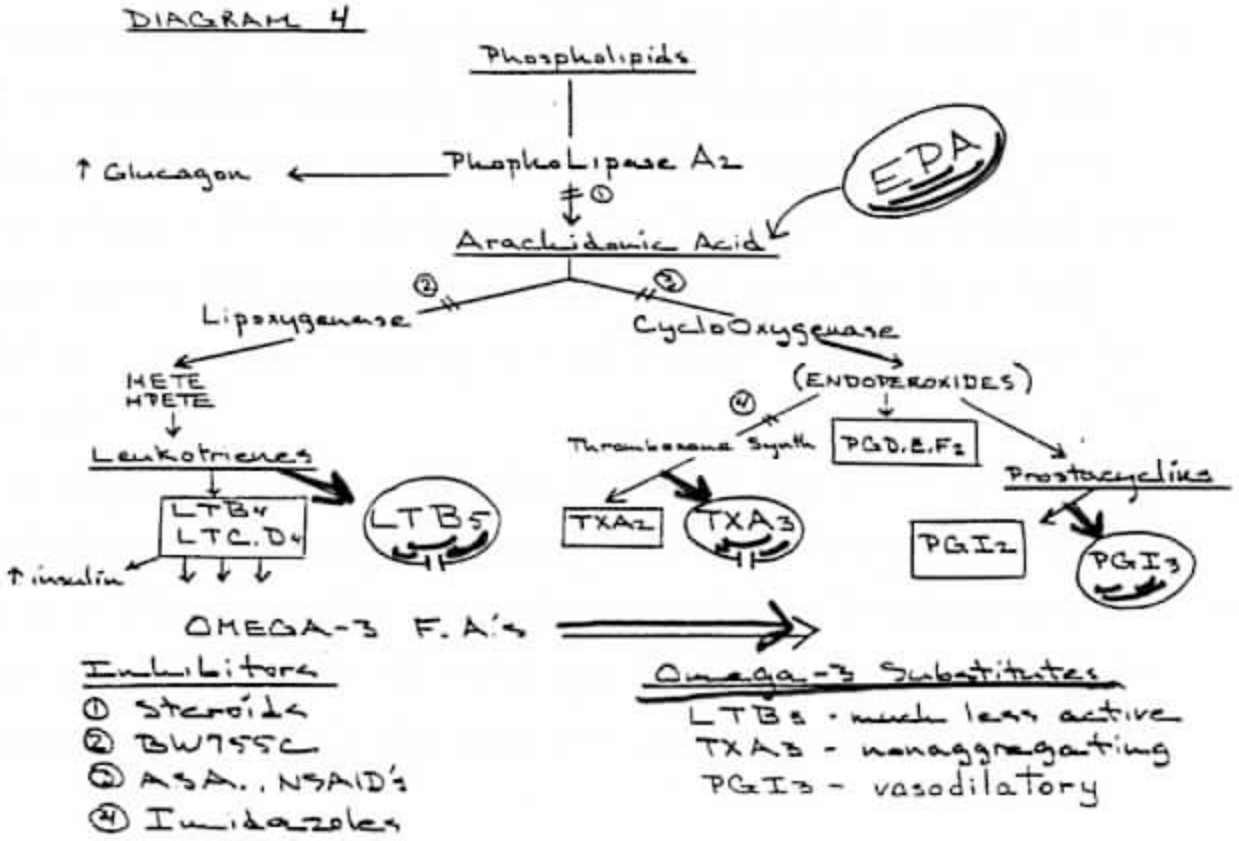


DIAGRAM 5

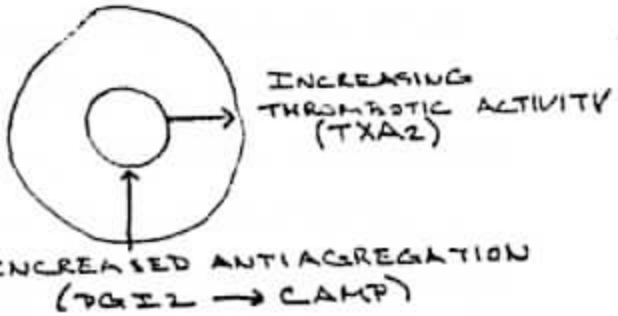


Diagram 5 can be used to conceptualize the normal homeostatic balance at the level of the blood vessel. The inner endothelial vessel wall synthesizes PGI2 de novo, and can produce PGI2 from platelet derived endoperoxides. In platelets, the primary product of the endoperoxides is TXA2, hence a homeostatic balance between the endothelial lining and the mobile platelets. Table 4 compares the effects of TXA2 and PGI2.

TABLE 4 Comparative Effects of Thromboxane A_2 and PGI_2

Thromboxane A_2	PGI_2
Platelets	Endothelial cells
Aggregator	Antiaggregator
Vasoconstrictor	Vasodilator
Inhibits adenyl cyclase	Stimulates adenyl cyclase
Injury	Homeostasis

Vascular irritation leads to platelet adhesion but not necessarily to thrombus formation. Apparently prostacyclin (PGI2) prevents aggregation at lower concentrations than that needed to prevent adhesion. Said another way, in a normal vessel in the absence of intimal injury, at low PGI2 concentrations, aggregation is preferentially inhibited locally and in the blood downstream from the source. When there is intimal injury, local TXA2 production from platelets overcomes the larger PGI2 concentration needed to prevent adhesion. Although the lungs contain a large mass of endothelial cells that can release PGI2 into the bloodstream. tissue metabolism is so rapid ($t\frac{1}{2}$ 2-3 min.) that after exogenous arterial infusion only 50% appears on the venous side[24].

As an aside, many have argued that if bleeding time is the key factor, prescription of aspirin on a prophylactic basis should be more protective. There is merit to this, but studies on aspirin use continue to be controversial[2,25,26]. The pro arguement hinges on the notion that low dose aspirin will inhibit TXA2 production at a level below that which will inhibit PGI2 production. The most

recent entry in the quest for this elusive dosage is the Physicians Health Study[2]. Thus, after a series of indepenent large scale studies were unable to show significant improvement in overall mortality after myocardial infarction at aspirin dosages of 500 mg. twice a day, 972 mg. once a day, or 300 mg. once a day[23], the dosage to be tested was reduced to 325 mg. every other day.

The group to be tested was choosen as follows: of the 261,000 physicians initially contacted, 112,000 responded and 59,000 agreed to participate. From this group were then excluded all physicians with a prior history of myocardial infarction, stroke or ischemic attack, cancer, current renal or liver disease, peptic ulcer, gout, contraindications to the use of, or current use of aspirin or aspirin like products. Of the remaining 33,000, one third were removed from the study after a trial run of 18 weeks for noncompliance with the study format. perhaps in no other study has a "healthy worker effect" been more successfully selected for. Indeed, after 4.8 years only 88 cardiovascular deaths were confirmed for the entire cohort, where 733 would have been expected within the remaining 22,000 doctors. Table 3 shows the breakdown of cardiovascular deaths according to treatment group. The Data Monitoring Board terminated the study because of the difference in deaths from acute myocardial infarction. However total cardiovascular deaths were equal in the aspirin and placebo groups. In no other subgroup of cardiovascular deaths did the aspirin group compare favorable with the placebo group. This data equally supports the contention that aspirin overwhelms the homeostatic balance inhibiting thrombembolic events in the short run, and encouraging the longer term, slower process of atherosclerosis.

Table 3. Cardiovascular Deaths According to Treatment Group.

Category of Cardiovascular Death (ICD Code)*	Aspirin	Placebo	Relative Risk	95% Confidence Interval	P Value
Acute myocardial infarction (410)	5	18	0.25	0.11–0.56	0.006
Stroke (430, 431, 434, 436)	6	2	3.00	0.75–11.98	0.16
Ischemic heart disease (411–414)	9	8	1.08	0.42–2.79	0.81
Sudden death (798)	13	9	1.49	0.65–3.43	0.40
Other cardiovascular (402, 424, 425, 428, 429, 440, 441)	10	6	1.79	0.67–4.76	0.31
Other cerebrovascular (431, 436)†	1	1	1.00	0.06–15.96	1.00
Total cardiovascular deaths	44	44	0.99	0.65–1.50	0.99

*ICD denotes International Classification of Diseases.
†Deaths occurring more than one year after the initial stroke.

NEJM, vol. 318: #4, p. 263, '88

The logical extension for the use of aspirin in the prophylactic treatment of cardiovascular disease would be the use of TXA2 synthetase inhibitor (see Diagram 4), but the accumulating endoperoxide precursors PGG2 and PGH2 can still activate platelets through the thromboxane receptor, according to Gerrard[22]. In either case, the loss of homeostatic balance remains troublesome.

The second physiological point is directed to the level of the cell membrane. One would expect that the introduction of fatty acid tails with increased chain length and number of double bonds into the membrane phospholipids would result in increased fluidity or entropy across the surface of the membrane. Studies to date have been contradictory[3,18]. The asymmetry of lipids across the bilayer membrane has been well established for erythrocytes as well as the plasma membrane of platelets and various heart cells[3,7]. This asymmetry allows for differential substrate stores for various cytosolic and membrane enzymes. The heart is one of the most responsive tissues to changes in dietary polyunsaturated fatty acids, in particular those of 20 and 22 carbon chain lengths. Inclusion of C20 and C22 n-3 fatty acids in the diet has been found to reduce arachidonic acid levels to as much as 50% of normal values[3]. These molecules do not pack with other fatty acyl chains as well as would fully saturated chains, resulting in an increase in the average surface cross sectional area per fatty acyl chain[3]. Paradoxically, the longer more unsaturated n-3 fatty acids have a shorter absolute length due to the shorter carbon-carbon double bond length and the increased angle between the single and cis-double bond as shown in Figure 6 .

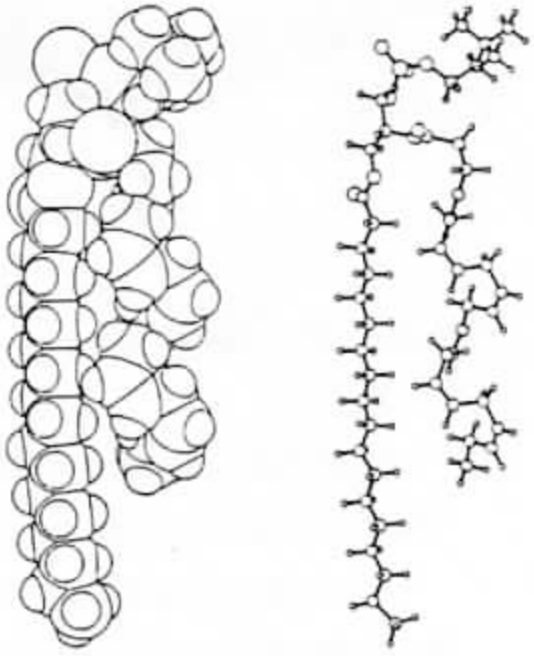


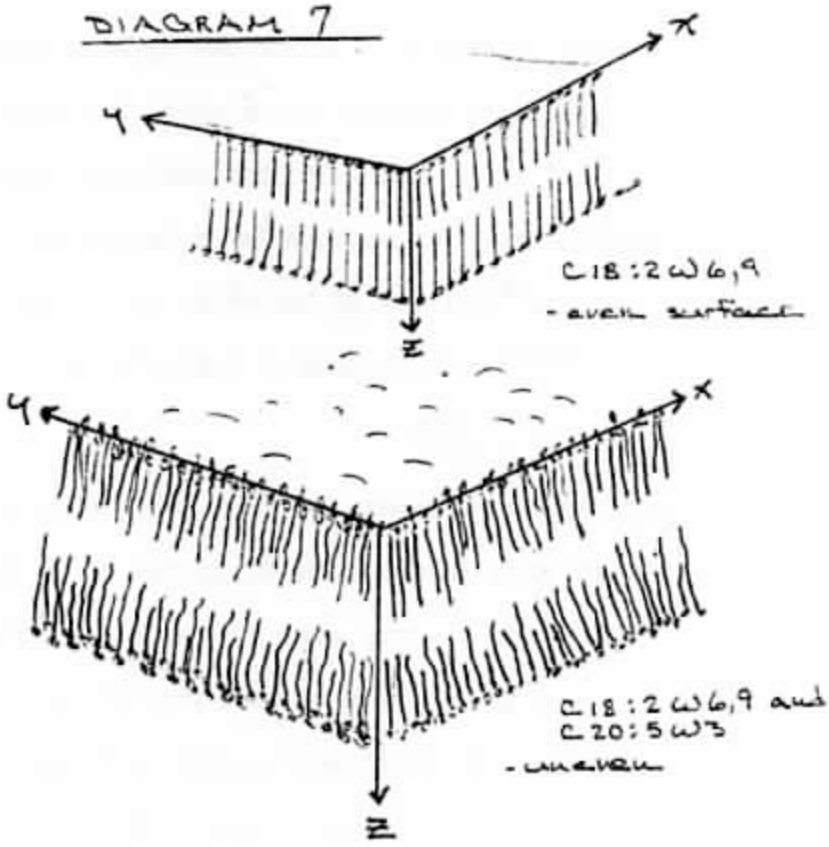
Fig. 6 Diagrammatic representations of 1-stearoyl-2-docosahexaenoyl-phosphatidylcholine (18:0/22:6-PC) drawn using the computer program 'Pluto' (by S. Motherwell), showing the effect of the six cis-double bonds on the sn-2 chain structural configuration (provided by S. Islam and S. Neidle).

Unfortunately, there is no simple correlation between membrane fluidity and

Biochim et BioPhys acta,v.779,p.114,'84.

fluidity and the phospholipid molar content of double bonds or double bond position. One useful piece of information is that the unsaturated fatty acids are carried primarily in the sn-2 position of the phospholipid, where Phospholipase A2 acts prefentially to separate fatty acids for the arachidonic acid cascade. The sn-1 position is primarily filled with saturated fatty acids allowing for conservation of the proportion of saturated to unsaturated fatty acids[3]. (see fig 6)

If you look at Diagram 7 you can visualize how differences in chain lengths may produce a variable potential space between the membrane layers about which little research has been done to date. However, viewing the XY plain, a few pieces of evidence support the contention that n-3 fatty acids produce a variability in the surface of the membrane.



First, EPA and DHA are preferentially integrated and degraded, which leads to the damping effect on the arachidonic acid cascade even when they are introduced in pharmacologic dosage[7]. This suggests that they are more vulnerable to Phospholipase A2.

Second, the phospholipids phosphatidylethanolamine, phosphatidylcholine, and cardiolipin concentrate asymmetrically with respect to the outer and inner sides of the bilayered membrane[7,3]. In a rat model Hock[7] found that various n-3 fatty acids also incorporated asymmetrically into the various phospholipid

groups extracted from rat myocardial tissue. Changes in phospholipid composition of aortic tissue were similar but with a 10-fold higher n-3/n-6 ratio. These membrane changes were induced by dietary supplementation with n-3 fatty acids over a four week period. After four weeks, acute and sham left coronary artery ligations were performed. After six hours the rats were sacrificed. Rats fed on an n-3 enhanced diet lost 405 less creatinine kinase from their left ventricular free wall than did control animals[7]. In a similar study Culp found significantly reduced thrombosis-induced infarct size in dogs subjected to a similar regimen[27].

Third, dietary supplementation with n-3 fatty acids appears to affect the number and function of some membrane proteins and receptors. Hock is currently preparing a paper showing a decreased A1 adrenergic receptor affinity in rats fed an n-3 fatty acid diet, that is not affected by aspirin[28]. Insulin receptor sensitivity appears to be effected in some studies[13,14].

Other Selected Animal Studies

Daoud et.al. in 1976 were able to show that advanced atherosclerosis in a swine model is susceptible to regression on removal of cholesterol from their diet[5]. Tenyears later in 1986 ina NEJM article by the same author, they were able to show inhibition of atherosclerosis by cod liver supplement in a hyperlipidemic swine model, and concluded that dietary cod liver oil retarded developement of coronary artery disease in their animal model[6].

Landymore et.al. looked at the effect of dietary supplementation with cod liver oil on venous autologous grafts implanted in the arteries of dogs. They found that intimal hyperplasia was largely prevented, while the combination of aspirin and dipyridamole was protective but not as effective[12].

Davis et.al. have found that a fish oil supplemented diet inhibits the developement of atherosclerosis in rhesus monkeys[36].

Human Studies

Early clinical studies tended to use large amounts of a fish oil equivalent on a few people for a relatively short period of time. Table 4 lists some representative results along with the number of subjects, the amount of EPA equivalents in grams/day, and the time space of the study. The most recently published study contains the largest number of subjects treated for the longest period of time.

Dehmer et.al., in the 9/22/88 NEJM, report on 82 male subjects who were treated with 3.2 gm/day of EPA one week prior to and 24 weeks after coronary angioplasty. They found a decrease in restenosis per patient from 46% to 19%[29]. The earlier review of cardiovascular effects of n-3 fatty acids by Leaf and Weber[1] mentions three other studies on the effect of n-3 fatty acids on restenosis after coronary angioplasty. Two of the studies found a reduction in the rate of restenosis[30,31] while a third did not[32].

Two preliminary studies on the effects of n-3 fatty acids on insulin resistance in Type II diabetics are intriguing but too small in scope to generate broad conclusions[13,14].

The very well controlled study by Kremer in the Annals of Internal Medicine provides convincing evidence that n-3 fatty acids have a salutory effect on subjective symptoms of acute rheumatoid arthritis[17].

Increased cholesterol levels are now accepted as one of the most important risk factors for CAD. Diets rich in EPA have generally been found to decrease serum triglycerides[9,11,33,37,38,40,44] and total cholesterol levels[9,11,38,40,44]. Effects on the various cholesterol lipoproteins have been inconsistant. VLDL levels have generally been found to be lowered[9,37], and this is reflected in studies finding lower synthesis of LDL[9,11,38,39]. In one study a paradoxical increase in LDL apoprotein B in both normal and hypertriglyceridemic subjects was found to accompany a decrease in triglycerides and total cholesterol;

both VLDL and LDL were found to be smaller and denser after dietary supplementation with fish oil[40].

Fish oil supplementation has been found to increase HDL receptors and the turnover of HDL[41,42], while HDL levels have been found to increase[11,46,48], decrease[9], or remain unchanged[43-45,47] in various studies.

A consensus of the effect of supplementation with fish oil on LDL and HDL levels in subjects with hypercholesterolemia and normal triglyceride levels has not emerged, but what is clear is that on a gram-for-gram basis, fish oils have a larger cholesterol and triglyceride lowering effect than equivalent dosages of n-6 vegetable oils[38].

Because of the increasing economic impact of cholesterol lowering agents, future studies should be read carefully for study design, cohort size, study length and side effect profiles.

TABLE 4 SELECTED LIST OF HUMAN STUDIES USING DIETARY SUPPLEMENTATION WITH OMEGA-3 FATTY ACIDS

STUDY *Reference	#, Type of Patients	Equivalent gm. of EPA	Time span for study	Effect	End Point
9. Phillipson, '85 NEJM	20 U.S. Hyper-triglyceridemics	20-30 g/day	4 weeks	⊕	↓ T. Chol., ↓ TG (triglycerides), ↓ VLDL
19. Knapp, '86	10 U.S. with PVD	10 g/d	4 wks	⊕	↓ TXA2 58%, ↑ EPA in RBC's and platelets
	2 U.S.	1 g/d	4 wks	⊖	normal TXA2 levels
10. Lorenz '83 Circulation	8 German male volunteers	10 g/d	3½ wks	⊕	↑ Bleeding time ↓ Platelet aggregation ↓ TXA2 ↓ B.P. (blood pressure)
33. von Schacky '85 J. Clin. Invest.	6 German male normals	2 - 8 g/d	20 wks	⊕	↓ TG ↓ Platelet aggregation ↓ TXA2
11. Singer, '85 Atherosclerosis	14 German male w/ Mild HTN	5 g/d	2 wks	⊕	↓ T. Chol., ↓ LDL, ↑ HDL, ↓ TG, ↓ LCAT ↓ B.P., ↑ uric acid
		2.8 g/d	2 wks	⊖	"insignificant"
17. Kremer, '87 Ann. of Int. Med.	40 U.S. with Rheumatoid arth.	4.5 g/d	14 wks	⊕	↑ subjective alleviation of acute rheumatoid arthritis ↓ LTB4 in neutrophils
34. Galloway, '85 Clin. Sci.	6 German normals	1.8 g/d	4 wks	⊕ ⊖	↑ bleeding time No altered platelet reactivity
8. Terano, '83 Athersclerosis	8 Japanese Normals	3.6 g/d	4 wks	⊕	↓ Platelet aggregation ↓ whole blood viscosity ↑ erythrocyte deformability
13. Popp-Snijders,'87 Diabetes Res.	6 NIDDM	3 g/d	8 wks	⊕	↓ TG ↑ Metabolic clearance rate of glucose Improved in vivo insulin sensitivity
14. Jones, D.B.,'87	15 NIDDM		12 wks	⊕	↓ Fasting blood sugar ↓ HbAlc, ↓ Insulin levels
29. Dehmer, '88 NEJM	82 U.S. males	3.2 g/d	25 wks	⊕	Decrease in post-angioplasty restenosis from 46% to 19%.

Conclusions

The purpose of this paper is not to debate the many individual study results, but to provide a basis for understanding a complex phenomena in an area of growing relevance to daily clinical practice.

At the molecular, cell membrane, organ and systemic vascular levels physiologic changes have been induced and quantified after dietary supplementation with fish oils. Numerous animal studies have shown a salutary effect on various aspects of the atherosclerotic process. In human studies, many individual results are contradictory, but some broad trends have emerged.

Dietary introduction of marine fish oils has an antiinflammatory effect via damping of the arachidonic acid cascade; an antiatherogenic effect via modulation of platelet function and blood lipid levels, and it may have a pro-insulin effect via some secondary mechanism involving membrane receptors and/or membrane protein function.

But what does this mean for the average beer drinking, hamberger eating, cigarette smoking, T.V. watching american male ? Clearly, persons unwilling to make modifications in their lifestyle will continue to be victims of atherosclerosis and its many ramifications, and will continue to consume a large portion of health services and resources. For physicians and patients interested in preventive health care, concern for probable beneficial effects of a generally benign intervention should not preclude careful analysis of each case, nor should they presume that this is a universal panacea. To date, no significant adverse side effects have been confirmed in any patient population to my knowledge. An area that remains relatively unexplored, is the effect of smaller amounts over extended periods of time.

If large scale double blind placebo controlled clinical studies continue to support some of the conclusions reached in this review, marine fish oils may well become the most essential dietary supplement for adult populations in industrial countries.

FOOTNOTES

1. Leaf A,Weber PC, Cardiovascular effects of n-3 fatty acids, N engl J Med 1988; v.318:549-57.

2. The Steering Committee of the Physicians' Health Study Research Group. Preliminary report: findings from the aspirin component of the ongoing Physician's Health Study, N engl J Med 1988;318:262-4.

3. Stubbs CD, Smith AD, The modification of mammalian membrane polyunsaturated fatty acid composition in relation to membrane fluidity and function, Biochim et Biophys Acta,1984;779:89-137.

4. Kromhout D, Bosschieter EB, Coulander CL, The inverse relation between fish consumption and 20-year mortality from coronary heart disease, N Engl J Med,1985;314:1205-9.

5. Daoud AS, Jarmolych J,Augustyn JM, Fritz KE, Singh JK, Lee KT, Regression of advanced atherosclerosis in swine,Arch Pathol Lab Med,1976;100:372-79.

6. Weiner BH, Ockene IS, Levine PH, Cuenoud HF, Fisher M, Johnson BF, Daoud AS, Jarmolych DH, Johnson MH, Natale A, Vaudreuil C, Hoogasian JJ, Inhibition of atherosclerosis by cod-liver oil in a hyperlipidemic swine model, N Engl J Med,1986;315:841-46.

7. Hock CE, Holahan MA, REibel DK, Effect of dietary fish oil on myocardial phospholipids and myocardial ischemic damage,Am J Physiol,1987;252:H554-60.

8. Terano T, Hirai A, Hamazaki T, Kobayashi S, Fujita T, Tamura Y, Kumagai A, Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in Healthy human subjects, Atherosclerosis,1983;46:321-31.

9. Phillipson BE, Rothrock DW, Connor WE, Harris WS, Illingworth DR, Reduction of plasma lipids, lipoproteins, and apoproteins by dietary fish oils in patients with hypertriglyceridemia,N Engl J Med,1985;312:1210-16.

10. Lorenz R, Spengler U, Fischer S, Duhm J, Weger PC, Platelet function, thromboxane formation and blood pressure control during supplementation of the western diet with cod liver oil, Circulation,1983;67:504-11.

11 Singer P, Wirth M, Voigt S, Richter-Heinrich E, Godicke W, Berger I, Naumann E, Listing J, Hartrodt W, taube C, Blood pressure- and lipid lowering effect of mackerel and herring diets in patients with mild essential hypertension, Atherosclerosis,1985;56:223-35.

12. Landymore RW,MacAulay M, Sheridan B, Cameron C, Comparison of cod-liver oil and aspirin-dipyridamole for the prevention of intimal hyperplasia in autologous vein grafts, Ann Thorac Surg,1986;41:54-7.

13. Popp-Snijders C, Schouten JA, HEine RJ, van-der-Meer J, van-der-Veen EA, Dietary supplementation of omega-3 polyunsaturated fatty acids improves sensitivity in non-insulin dependent diabetes,Diabetes Res,1987;4(3):141-7.

14. Jones DB,Haitas B, Bown EG, Carter RD, Barker K, Jelfs R, Turner RC, Mann JI, Prescott RJ, Platelet aggregation in non-insulin dependent diabetes is associated with platelet fatty acids, diabetic Med,1986;3(1):52-5.

15. Robertson RP, Prostaglandins, glucose homeostasis and diabetes mellitus, Ann Rev Med, 1983;34:1-12.

16. Pek SB, Walsh MF, Eicosanoids as regulators of pancreatic islet hormone secretion, Advances in Prostaglandin, thromboxane and leukotriene research, 1985;13:221-29.

17. Kremer JM, Jubiz W, Michalek A, Rynes RI, Bartholemew LE, Bigaouette J, Timshalk M, Beeler D, Lininger L, Fish-oil supplementation in active rheumatoid arthritis,1Annals of Internal Medicine,1987;106:497-503.

18. Lee TH, Hoover RL, Williams JD, SPerling RI, Ravalese J, Spur BW, Robinson DR, Corey EJ, Lewis RA, Austen KF, Effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene generation and neutrophil function, N Engl J Med,1985;312:1217-24.

19. Knapp HR, REILLY IA, alessandrine P, Fitzgerald GA, In vivo indexes of platelet and vascular function during fish oil administration in patients with atherosclerosis, N Engl J Med,1986;314(15):937-42.

20. Crosset M, Lagarde M, In vitro incorporation and metabolism of eicosapentaenoic and docosahexaenoic acid in human platelets- effect on aggregation, Thromb Haemost,1986;56:57-62.

21. Walton I, The compleat angler, Penguin Books,1985, New York.

22. Kromann N, Green A, Epidemiolgical studies in the Upernavik District, Greenland, Acta Med Scand,1980;208:401-6.

23. Horrobin DF, Low prevalences of coronary heart disease, psoriasis,asthma and rheumatoid arthritis in eskimos: are they caused by a high dietary intake of EPA, a genetic variation of essential fatty acid (EPA) metabolism or a combination of both?, Medical Hypotheses,1987;22:421-28.

24. Moncada S, Vane JR, Arachidonic acid metabolites and the interactions between platelets and blood vessel walls, N Engl J Med,1979;300(20):1142-47.

25. Cohen LS, Management of patients after Myocardial infarction, Hospital Practice, April 15,1987,p.149-73.

26. Gerrard JM, Platelet aggregation: cellular regualtion and physiologic role, Hospital Practice, Jan 15,1988,p. 89-108.

27. Culp BR, Lands WEM, Lucchesi BR, Pitt B, Romson J, The Effect of dietary supplementation of fish oil on experimental myocardial infarction, Prostaglandins,1980;20:1021-31.

28. Hock, Carl, personal correspondence.

29. Dehmer JD, Popma JJ, van den Berg EK, Eichorn EJ, Prewitt JB, Campbell WB, Jennings L, Willerson JT, Schmitz JM, Reduction in the rate of early restenosis after coronary angioplasty by a diet supplemented with n-3 fatty acids, N Engl J Med, 1988;319(12):733-40.

30. Grigg LE, Kay T, Manolas EG, Hunt D, Valentine PA, Does Mas-EPA lower the risk of restenosis after PTCA? A prospective randomized trial, Circulation, 1987;76:Suppl 4:IV-214, abstract.

31. Schmitz JM, van den Berg EK, Prewitt JP, Malloy CR, Willerson JT, Dehmer GJ, Dietary supplementation with n-3 fatty acids may reduce the rate of restenosis after coronary angioplasty, Clin Res,1987;35:6A.abstract.

32. Slack JD, Pinkerton CA, Van Tassel J, et.al., Can oral fish oil supplement minimize re-stenosis after percutaneous translumenal coronary angioplasty? J Am Coll Cardiol, 1987;9:64a.abstract.

33. von Schacky C, Fischer S, Weber PC, Long term effects of dietary marine n-3 fatty acids upon plasma and cellular lipids, platelet function, and Eicosanoid formation in humans,J Clin Invest,1985;76:1626-31.

34. Galloway JH, Cartwright IJ, Woodcock BE, Greaves M, Russel RGG, Preston FE, Effects of dietary fish oil supplementation on the fatty acid composition of the human platelet membrane: demonstration of selectivity in the incorporation of eicosapentaenoic acid into the membrane phospholipid pools, Clinical Science,1985;68:449-54.

35. Chadwick, Henry, The Early Church, Penguin Books, 1981,p.255.

36. Davis HR, Bridenstine RT, Vesselinovitch D, Wissler RW, Fish oil inhibits developement of atherosclerosis in rhesus monkeys,Arteriosclerosis,1987;7: 441-9.

37. Sanders TAB, Sullivan DR, Reeve J, Thompson GR, Triglyceride-lowering effect of marine polyunsaturates in patients with hypertriglyceridemia, Arteriosclerosis, 1985;5:459-65.

38. Harris WS, Connor WE, McMurphy MP, The comparative reductions of the plasma lipids and lipoproteins by dietary polyunsaturated fats: salmon oil versus vegetable oil, Metabolism, 1983;32:179-84.

39. Illingworth DR, Harris WS, Connor WE, Inhibition of low density lipoprotein synthesis by dietary omega-3 fatty acids in humans, Arteriosclerosis, 1984;4:270-5.

40. Sullivan DR, Sanders TAB, Trayner IM, Thompson GR, Paradoxical elevation of LDL apoprotein B levels in Hypertriglyceridemic patients and normal subjects ingesting fish oil, Atherosclerosis,1986;61:129-34.

41. Nestel P, Topping D, Marsh J, et.al., Effects of polyenoic fatty acids (n-3) On lipid and lipoprotein metabolism. In: Lands WEM,ed. POlyunsaturated fatty acids and eicosanoids. Champagne Ill.: American Oil Chemists Society, 1987;94-102.

42. Roach P, Kambouris A, Trimble R, Topping D, Nestel P, Fish oil downregulates the low density lipoprotein receptor and upregualtes the high density lipoprotein receptor of rat liver, Arteriosclerosis,1987;7:533a.abstract.

43. Bronsgeest-Schoute HC, Gent CM van, Luten JB, Ruiter A, The effect of various intakes of n-3 fatty acids on the blood lipid composition in healthy human subjects, Am J Clin Nutr,1981;34:1752-7.

44. Lossonczy TO von, Ruiter A, Brongeest-Schoute HC, Gent CM van, Hermus RJJ, The effect of a fish diet on serum lipids in healthy human subjects, Am J Clin Nutr,1978;31: 1340-6.

45. Fehilly Am, Burr ML, PHillips KM, Deadman NM, The effect of fatty fish on plasma lipid and lipoprotein concentrations, AM J Clin Nutr,1983;38:349-51.

46. Sanders TB, Vickers M, Haines AP, Effect on blood lipids and haemostasis of a supplement of cod liver oil, rich in eicosapentaenoic and docosahexaenoic acids in healthy young men, Clin Sci,1981;61:p.317.

47. Mortensen JZ, Schmidt EB, Nielson AH, and Dyerberg J, The effect of N-6 and n-3 polyunsaturated fatty acids on haemostasis, blood lipids and blood pressure, Thromb Haemost (Stuttgart),1983;50:p.543.

48. Saynor R, Verel D, Gillot T, The long term effect of dietary supplementation with fish lipid concentrate on serum lipids, bleeding time, platelets and angina, Atherosclerosis,1984;50:p.3.