

# Fish is More Than a Brain Food

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**Abstract.** From merely being cod liver oil taken for vitamins A and D, fish oils have moved into the center stage of fatty acids in nutrition. The analytical work starting in 1950 provided the means to recognize the long-chain and truly essential n-3 polyunsaturated fatty acids vital for retinal, neurological and cellular membrane functions in our bodies. The "Eskimo" studies of twenty years ago have also now been followed scientifically for two decades, into our recognizing fish and shellfish as highly desirable food sources of these n-3 fatty acids for cardiovascular benefits.

**Keywords:** cardiovascular function, eicosapentaenoic, docosahexaenoic, neural function

## 1 INTRODUCTION

The folklore about fish being a brain food was imparted to me about 1934 by my maternal grandmother. As always, she was right. I have been able to trace this saying to the middle of the 19<sup>th</sup> century, when organic solvents became available and German scientists were able to extract things like cod fish muscle and human brains. The grey pastes that resulted from these two materials were rather similar, since they were dominated by phospholipids with a substantial proportion of highly unsaturated fatty acids, both materials not yet known to science.

Fish oils were used as industrial chemicals for a hundred years though they were not understood in detail. Their uses were partly based on paints and linoleum, materials where the fatty acids we now know to be highly unsaturated could crosslink into polymers. Hydrogenation for margarine was possible from about 1900, but the quality and purity of the raw material was dubious. Sulphur compounds, for example, from the amino acids of fish protein left too long before oil production, poisoned the catalysts. At the time whale oil was preferred as it was a purer raw material, and even as late as 30 years ago seal oil commanded a higher price than fish oil in Canada for margarine and shortening manufacture because of quality and ease of manufacture. Today we know that this procedure applied to marine oils was wasting highly unsaturated fatty acids potentially valuable in our diets.

In 1952 Bailey, Carter and Swain published Bulletin 89 of the Fisheries Research Board of Canada. By this time common terrestrial fatty acids such as oleic, linoleic and alpha-linolenic had definite structures and could be discussed for foods, but the long-chain, highly unsaturated fatty acids of marine origin were listed under a variety of names (usually related to the species of fish providing the oil that was examined) and an even greater assortment of positions for the ethylenic bonds.

Two teams resolved most of the significant issues. E. Klenk, in Germany, published a series of papers in 1958-1962 accurately defining several marine polyunsaturated fatty acids such as all-cis-6,9,12,15-octadecatetraenoic fatty acid (18:4n-3, now called stearidonic). The rapid implementation of chromatographic technology, especially thin-layer and gas-liquid chromatography, and adequate funding by the Rockefeller Institute, led to a group there publishing an almost complete analysis of the fatty acids of menhaden oil (Farquhar et al., 1959). The conceptual problem in identifications was that everybody tried to relate these through the positions of the ethylenic bonds relative to the carboxyl group.

By 1962 H.J. Thomasson had realized the importance of the other end of the chain (Thomasson, 1962) and with this useful addition most of the work of the biochemistry group of the Hormel Institute and elsewhere on 'essential fatty acids' fell into place. Personally I benefitted enormously from publications of these authors because Halifax, Nova Scotia, Canada, was remote from other centres doing research into highly unsaturated animal and marine fatty acids. Standards were scarce and expensive. With the data available I was able to organise almost all polyunsaturated fatty acids of marine organisms into structural groups, thus easily identifying unknown peaks in one analysis on any GLC column. For example separation factors for ethylenic bonds could be generated from the almost any readily available vegetable oil:

Structure	Ä position	relative retention time	separation factors		
			3/6	6/9	3/9
18:3n-3	9,12,15	1.76	-	-	-
18:2n-6	9,12	1.35	1.30	-	-
18:1n-9	9	1.12	-	1.21	1.57

In my GLC runs of marine lipid fatty acids a large peak at the

end was sure to be docosahexaenoic acid, so one could look for obvious peaks eluting earlier based on the above factors from the vegetable oil analysis on the same column. In this case:

22:6n-3	4,7,10,13,16,19	9.55	-	-	-
22:5n-6	4,7,10,13,16	7.43	1.28	-	-
(22:4n-9)	(4,7,10,13)	(6.17)	-	1.21	1.55

No peak could be found near the predicted 22:4n-9 position in the methyl esters of fish oil fatty acids so probably it would not exist. A peak observed adjacent to and before 22:6n-3 (DHA, docosahexaenoic acid) was probably 22:5n-3 (DPA, docosapentaenoic acid). From it 22:4n-6 could be predicted by the same procedure, and the obvious 20:5n-3 (EPA, eicosapentaenoic acid) peak predicted 20:4n-6, arachidonic acid, and 20:3n-9, observed in cases of essential fatty acid deficiency in mammals and called Mead acid. The process could also be reversed, for example from 20:1n-9 one could predict where 20:2n-6 and 20:3n-3 would be found.

The same retention data could be plotted graphically as parallel line systems on semi-log paper, permitting identification between chain lengths for fatty acids of different numbers of carbon atoms and the same number of ethylenic bonds, for each of the n-3, n-6 or n-9 structures. These two technologies were published in 1963 (Ackman 1963a; 1963b).

In general terms the various fish oil monoethylenic isomers could be grouped together by plotting as n-11, n-9, n-7 and even n-5.

The overall result was the identification of the fatty acids shown in Figure 1, including the exotic n-1, n-4, n-7 series of polyunsaturated fatty acids of algal origin identified by Klenk and colleagues in herring and in menhaden oil by the Rockefeller team. Figure 2 shows the importance of these fatty acids in algae and their lesser importance in menhaden oil.

By 1966 we had capillary GLC capability and the structurally novel monoethylenic fatty acids of Figure 1 could be readily identified. Ironically about that time (1964) in Great Britain Hilditch and Williams published a book, "The Chemical Constitution of Natural Fats" which is known to many of you.

It was the first book to explain the chemistry of most fats and oils in terms of specific fatty acids. Unfortunately fish oils in nutrition were not widely understood or examined as foods except as sources of vitamins A and D. M.E. Stansby benefitted from the output of the Saltenstall-Kennedy program that funded much fish oil biochemical and nutritional research to edit a new and very useful book on the subject (Stansby, 1967).

At the same time the cholesterol dogma began to terrify the population of western society and the edible oils industry used

the benefits of linoleic acid in lowering serum cholesterol to push vegetable oils such as corn and soybean into the marketplace. In Canada, Health and Welfare Canada refused to put the newly developed canola oil on a list of recommended edible oils because it had only 20% of linoleic acid. They did not regard the accompanying 10% of alpha-linolenic acid as useful or essential in any way. This type of mental block was the basis of the extraordinary delay in any type of n-3 fatty acid achieving recognition as "essential" (Holman 1998) and it persists to this day in current approved labelling of foods.

Although I have not mentioned saturated fatty acids, in marine oils and fats the even-carbon series 14:0-16:0-18:0 predominate, with minor amounts of 15:0 and 17:0, and of iso and anteiso C15 and C17 chain lengths. These total 15-30%. All of the saturated acids can be biosynthesized by any fish or shellfish, and this is also true of 16:1n-7 and 18:1n-9, both originating in a  $\Delta^9$  desaturase operating on 16:0 or 18:0 respectively. Many fish oils have some elongation of 16:1n-7 to 18:1n-7, the latter usually being about a quarter of the 18:1n-9 isomer. The 20:1 fatty acids are to some extent created by elongation of the two 18:1 isomers but with capillary GLC a small proportion of 20:1n-11 is often seen accompanying 20:1n-9 and 20:1n-7. The 22:1 monoethylenic fatty acids have a mainly different origin, in the wax esters of copepods (Ratnayake and Ackman 1979a;1979b). For unknown reasons the structure of the principal fatty alcohol of many copepods may be 22:1n-11, and this is converted to the corresponding fatty acid in the gut mucosa of predatory fish such as capelin, herring or mackerel. Some 22:1n-9 and even 22:1n-7 may be present, probably originating in the C18 and C20 monoethylenic isomers. Table 1 compares 14 fatty acids of menhaden oil with those of herring oil, and of the fatty acids of muscle phospholipids from farmed Atlantic salmon and Atlantic cod.

Certain generalities are apparent. In the fish body oils saturated acids are variable, and the proportions are inversely related to 20:1 and 22:1. A range of 20-35% is a reasonable expectation.

In the two oils of Table 1 EPA exceeds DPA, although in other fish body oils such as those of pelagic tuna the proportions are often 5% EPA accompanied by as much as 20% DHA. The range for the total of these two highly unsaturated fatty acids in common fish oils is about 13-25%. Winterizing menhaden oil leads to removal of triacylglycerols rich in saturated fatty acids and total EPA and DHA can then be pushed to 30%.

The two phospholipids contain about 22%-25% saturated acids and 16-26% monoethylenic acids. The salmon were fed a diet rich in herring oil, accounting for the 8% total for 20:1 and 22:1 in the muscle phospholipids. Usually these are less important in phospholipids and a figure of 2% is more typical. Arachidonic acid (20:4n-6) is not well represented in these cold-water marine species. As little as 1-2% of 18:2n-6 is found in these oils (not shown) and a similar amount of 18:3n-3

would be found in the phospholipids. The important items in human nutrition are the highly unsaturated fatty acids EPA and DHA, usually totalling around 40% of the fatty acids of fish phospholipids.

The question most asked about omega-3 fatty acids in fish is the wrong question. Invariably somebody wants the percentages in the total fatty acids. This is part of the numbers game in selling a product. What they should really ask for is the g/100 g figure for edible parts. Fortuitously, for most marine fish, muscle will contain about 0.8% phospholipids. The phospholipid in 100 g of edible muscle may contain approximately 75% or 0.6 g of fatty acids, so the available EPA and DHA from that source will be about 40% of that or 240 mg. Most one-gram fish oil capsules contain 150-300 mg total omega-3 fatty acids so one serving of lean fish equates with one fish oil capsule.

Supposing a salmon fillet with 11% extractable fat is served, then of this approximately 0.8 g will be phospholipids and 10.2 g will be triglycerides. Using the figures in Table 1 these will contain the same muscle phospholipids ( $18:4n-3 + 20:5n-3 + 22:5n-3 + 22:6n-3 = 43.6\%$ ), supplying 260 mg per 100 g of salmon muscle. Salmon oil is not especially high in these fatty acids, but the 10 g of matching triacylglycerols (Polvi et al, 1992) will have ( $1.3 + 2.5 + 1.0 + 5.5 = 10.3\%$ ) of omega-3 fatty acids, so the oil supplies nearly 1 gram of additional omega-3 fatty acids per 100 g, for a total of 1.26 g. Assuming no loss of oil on cooking, a serving of "oily" salmon will contain much more omega-3 fatty acids than are provided by several ordinary fish oil capsules. That is why a Government committee recommendation in Great Britain was to eat fish at least twice a week, and of these one serving should be of oily fish (U.K. Department of Health 1994).

## 2. Freshwater Fish

Most of the fish in North America's lakes and rivers are descendants of sea fish that recolonized these waters after glaciations. Some, like salmon, spawn in freshwater and return to the sea, and some, like arctic char, reverse the process. Basically they therefore share the same fatty acids except for a little more emphasis on the n-6 fatty acids when in freshwater. In marine fish n-6 fatty acids these may total only 3-5%, but in purely freshwater fish it could be 5-10%. There are still plenty of n-3 fatty acids in the muscle cells, but in warm water species such as carp and channel catfish depot fats are low in EPA and DHA. They are now marketed mostly as

farmed fish and the diets employed can somewhat alter these particulars

## 3. Shellfish

A great misunderstanding arose four decades ago. Molluscs such as oysters, mussels, clams etc. are lean, lipid ranging from 1-3% (Table 2), because their energy reserve is glycogen, not triacylglycerols, so there are few fatty acids. Unfortunately the cells and their membranes require sterols as structural components. Most have only 40% cholesterol in the sterols and the other 60% is made up of various algal sterols. The latter are now suddenly healthy in products such as Benecol<sup>7</sup> and Take Control<sup>7</sup>. However at that time methods for sterol analysis were poorly developed and the confusion on "the question to be asked" led to the 40% figure alarming nutritionists who must have thought that it was 40% of the total lipid. Lists of food acceptable for people with elevated cholesterol therefore banned "shellfish". In fact molluscs may have only 35-56 mg of cholesterol per 100 g sterols, or about the same as beef. However lobster and crab meat have about 75 mg/100g, and shrimp up to 150 mg/100g (Krzynowek and Panunzio, 1989).

The fatty acid contents of shellfish muscle are also low because the lipid is low, and Table 2 shows that EPA is often higher than DHA because of the algal diet of bivalves. The total available n-3 of this group is however not too dissimilar from that of the phospholipids of the lean fish of Table 1, or about 300 mg/100 g eaten. More details of this topic will be found in papers by Gordon (1982) or King et al. (1990). Shellfish provide variety and would be more popular if safety was not an issue in some places. The hazards are twofold. One is of course bacterial or vibrio contaminations, reflecting human activities and waste, and the other is toxins derived from algae. The latter have recently been recognized in various countries around the world where they were not suspected before, suggesting climatic and oceanographic changes. Fatty acids such as EPA (20:5n-3) in free acid form have in fact been suggested as factors in diarrhetic shellfish poisoning, but clinical evidence is scanty.

## 4. What about brain food?

It is strange that about a decade ago the neurofunctional implications of n-3 fatty acids were catapulted into scientific but not necessarily public interest. From rhesus monkeys (Neuringer et al, 1996) to studies on visual responses to stimuli in human infants (Carlson, 1997) was a considerable step. The results of providing n-3 fatty acids were at times the basis of acrimonious disputes on methods of assessment, but a recent meta-analysis (San Giovanni et al 2000) concludes that in early development of the human visual system there are significant

differences for DHA supplemented and DHA-free formulas. It was strange that few have emphasized that the nursing infant receives DHA and a lesser amount of EPA in human milk, probably reflecting that available in the mother's body (Ackman, 1999). However the importance of this low level of DHA, found at about 0.29% of fatty acids, was masked by the relatively large amounts (0.5-0.7%) of arachidonic acid (20:4n-6), itself an important source of eicosanoids (Al et al., 1995a).

In this less than perfect world one study with fish oil showed a brief arresting of infant growth that was attributed to the competition between an excessive intake of 20:5n-3 and the natural level of 20:4n-6 (reviewed by many authors, for example Birch et al. 1998). There is also a need to distinguish studies with term and pre-term infants. Although pregnant women should avoid fish contaminated with heavy metals, pesticides, or natural toxins, the need to provide DHA to the infant brain in the last trimester should be an overriding consideration favouring fish consumption (Al et al. 1995a; 1995b).

It can be demonstrated in mice that even old mice can benefit from dietary DHA (Lim and Suzuki, 2000). The problem is that humans are too large to be effective as experimental animals. The increase in the aging population with mental problems suggests that something basic should be investigated and deficiencies in peroxisomes have been suggested in this connection (Périchon and Bourre, 1996). The reason is that they play a vital role in the biosynthesis of DHA. Although conservation of polyunsaturated fatty acids seems an obvious practice the brain is difficult to investigate. Fish consumption data is however available and the proportions of degenerative brain diseases in different situations or countries should be investigated.

## 5. EPA versus DHA

Nobody wants to die, but it is inevitable. The classic heart attack due to blocking of the coronary artery is often survivable with prompt treatment. This could be called phase I of the exit process and can take 60 years, depending on genes and lifestyle. If the genes are bad 40 years will do it. The 1985 Zutphen study (Kromhout et al. 1985) was the first to show that a cross-section of "normal" people could survive longer by regularly consuming fish. The Eskimo studies of Bang and Dyerberg (1980) and Bang et al. (1980), supported by the basic research of the Burroughs Wellcome Co., indicated that EPA (20:5n-3) was the beneficial factor. In effect, in suitable subjects it helps the blood vessel walls stay elastic and free of deposits. The DHA appeared to help somewhat by replacing some of the arachidonic acid in the blood platelets and thus reducing risk of clotting. It required another decade before Australian scientists (Charnock et al.

19xx) picked up on the n-3 fatty acids as factors modifying electrical problems leading to ventricular tachycardia (arrhythmia). Their work appeared to show that this was phase II of many cardiac deaths but was confused at first by the use of a fish oil high in DHA. Later Dr. Alexander Leaf and colleagues patiently sorted out the movement of signals (Kang and Leaf, 1996) and showed that most polyunsaturated fatty acids have some beneficial effects. The fact that the myocardial tissue was normally high in 22:6n-3 (DHA) suggests that it should have a preferential functional role in this situation.

There are simply too many papers favourable to the clinical use of fish oils to review in this short article. They provide both EPA and DHA in one shot, and the body actually can interconvert them if one is more available than the other.

One company selling fish oil for use in foods has emphasized that in modern North America we have a shortfall of intake of 1 g per day of EPA and DHA. This is probably in agreement with the major "natural" diet studies intakes where fish were involved, such as the Zutphen study already cited, the U.K. DART study (Burr et al. 1989, Burr 1989), and with capsules the more recent GISSI trial (1999).

## 6. Omega-3 Fatty Acids: Is it time for clinical implementation?

I have appropriated this heading from a short article by O'Keefe and Harris (2000) in the American Journal of Cardiology. That is the principal decision that modern medicine should be making. The problems is that a major pharmaceutical firm that once cheerfully sold fish oil capsules for 10 cents each now markets cholesterol-lowering drugs for several dollars for each pill. All the major pharmaceutical firms sell similar products. These products have various effects on HDL, LDL or other types of lipoproteins, and also various side-effects of uncertain importance. While the U.S. National Library in Bethesda was monitoring research publications, they were easily able to collect annually about 700 literature citations on fish oils and cardiovascular disease. From such publications views have arisen to indicate that fish as food and fish oils in capsules share benefits that are risk-free (Simopoulos, 1997). The U.S. FDA considers that 3 g per day of EPA + DHA is safe. To consume this is difficult, even with capsules containing 50% of these two fatty acids, but a meal of 200 g of farmed salmon might do it. Of course some DHA is available from eggs and even the white breast of chicken is an important source in most of the world.

## 7. Conclusions

Fish and shellfish provide an almost unlimited variety of fatty acids with beneficial role in human health. There are no risks

attached to these fatty acids and generally, except for deep-fried portions, they are relatively low in fat compared to many cuts of farm meats.

## 8. References

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