The Absorption of Fish Oils and Concentrates[1]

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Both preventive and curative therapies have created a considerable demand for eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids. The most common sources for ω3 fatty acids are fish oil. The concentrations of EPA and DHA in commercial oils, after modest enrichment, reach about 300 mg/g; alternative technologies can produce reasonably priced fish oils containing 400 or even 500 mg/g of ω3 acids. When the acids are liberated from the glycerides, concentrates of ethyl esters or free acids with 65 to 70% total ω3 fatty acids (at least 50% EPA + DHA) are readily prepared. Difficulties have arisen because most clinical trials have used fish oils of unspecified composition, and some trials are now based on either ethyl esters or free acids. There are at least three different, but not mutually exclusive, absorption routes in humans, namely the preduodenal route, the lymphatic route *via* chylomicrons, and the route *via* the portal vein to the liver. This makes it difficult to compare results. The difficulty in obtaining dose-related clinical data may in part be due to the form in which the ω3 acids are offered and due in part to the natural presence of these fatty acids in the body. The nontriglyceride forms, especially the free acids, have been advocated for standardization of trials to facilitate interlaboratory comparisons.
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The epidemiology of the health benefits of ω3 fatty acids in Greenland Eskimos (1-5) has been the source of much discussion. Excluding difficulties in diagnosis and *post mortem* evaluations (5), the effect of dietary ω3 fatty acids could be attributed to an extremely high intake of long-chain ω3 fatty acids and to a possible role of ω3 docosapentaenoic acid (DPA).

It is well to remember that the studies on Greenland Eskimos were started nearly a decade before the first publication (6) on the potential role of ω3 fatty acids appeared in 1979. At the same time, a survey of Alaskan Eskimo consumption of fats and fatty acids was the subject of a U.S. doctoral thesis in 1973 and provided a comparable data base (7). Table 1 provides the proportions of the three important long-chain fatty acids in fats of several marine mammals from Alaska, the Arctic and the Atlantic coast of Canada. Other evidence has been published on fats of northern food sources (7,9,11), but fish fats basically have relatively low levels of DPA (12) compared to fats of seals and whales.

DPA and marine mammal fats. The function of DPA in marine mammal fat has been obscure, and it is not known to be linked to an eicosanoid in the same way as is eicosapentaenoic acid (EPA). In fact it seems rational to propose that

TABLE 1

Proportions (wt/wt% of total fatty acids) of Three Long-Chain ω3 Fatty Acids in Blubber Fats of Alaskan Marine Mammals, and of Atlantic Harbor Seal, Ringed Seal and Finwhale

Marine mammals	Fatty acid[a]			
	EPA	DPA	DHA	Reference
Walrus (Pacific) *(Odobenus rosmarus)*	7.63	5.99	5.83	(7)
Bearded seal (Pacific) *(Erignathus barbatus)*	8.59	5.99	6.73	(7)
Pacific harbor seal *(Phoca vitulina richardi)*	8.67	4.92	8.33	(7)
Pacific bowhead whale *(Balaena mysticetus)*	8.52	3.23	5.22	(7)
Atlantic harbor seal *(Phoca vitulina)*	4.35	3.95	8.09	(8)
Atlantic finwhale *(Balaenoptera physalus)*	3.72	2.28	6.23	(10)
Ringed seal *(Phoca hispida)*	9.8	5.9	10.0	(9)

[a]EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid, DPA, docosapentaenoic acid.

in most fatty tissue the Δ4,5 desaturase postulated to convert DPA to docosahexaenoic acid (DHA) is relatively inactive. Brain and neural tissues are clearly exceptions, but in humans relatively little work has been done on EPA-DPA-DHA proportions in whole body studies (13) as compared to that on the blood platelet phospholipids (14) which may, however, not be representative. Instead it has become increasingly apparent that DPA is a temporary storage site for surplus EPA. The hypothesis that DHA has no specific role in movine mammal fats could also account for the accumulation of DPA in the seal fats (Table 1). In the fish eaten by seals, the DPA level is usually only 2-5% of combined EPA and DHA (12).

Triglycerides. Long-chain ω3 fatty acids, especially DHA, are reputedly located in the *sn*-3 position of marine mammal triglycerides, as distinct from the fish oils where DHA is found mainly in the *sn*-2 position, (15-18). H. Brockerhoff (cited in ref. 16) published much of the data and theory on this difference.

The fats in the foods eaten by humans have been dealt with by various authors (19,20). The major fat types are triglycerides, followed in nutritional importance by phospholipid or other "polar" lipid and finally by free fatty acids. Ethyl esters will also be included here.

In small populations consuming a high level of marine fats, pros and cons exist as to the benefits of a high ω3 fatty acid intake (21-23). In other groups (24,25), it is difficult to demonstrate health benefits of eating fish (26) on a par with those of the Kromhout study (27). The latter study was supported by retrospective examination of fish consumption in other diet-health studies (28,29). In the recent spectacular extension of survival in patients advised to eat more fatty fish three times a week (30), the most interesting result was that the benefits became apparent in just over three months. In the study by Burr *et al.* (30), fish oil cap-

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Abbreviations: DHA, 4,7,10,13,16,19-docosahexaenoic acid, 22:6ω3; DPA, 7,10,13,16,19-docosapentaenoic acid, 22:5ω3; EPA, 5,8,11,14,17-eicosapentaenoic acid, 20:5ω3; FFA, free fatty acid(s); HDL, high density lipoprotein; MG, monoglyceride(s); PUFA, polyunsaturated fatty acid(s); TG, triglyceride(s).

sules were provided as an alternative for those patients not wishing to consume large quantities of fish.

Even fish oil studies of short duration can be relevant. For example, Boyce and Fordyce (31) fed cod liver oil for 14 d as either a bolus of oil while fasting or with lunch. The subjects then had a washout period of 14 d and then reversed the consumption pattern. The ratio of high density lipoprotein (HDL) cholesterol to total cholesterol changed according to the time of consumption. A favorable result, an increase in HDL levels, followed from taking capsules with meals.

Free acids in the diet are totally absorbed, and fatty acids of triglycerides are usually absorbed to the extent of 90% or more (32,33). The distribution of long-chain ω3 fatty acids on the glycerol moiety differs between fish and seals or other marine mammals (15), including seal milks (34) but is of course limited to a total of about 30 mole% for all ω3 fatty acids in all natural triglyceride (17). Thus U.S. menhaden oil (see Table 2) might have (in wt%) 9.4% DHA, 2.1% DPA, 14.8% EPA and 3.3% 18:4n-3 (35). By comparison the ubiquitous MaxEPA (Seven Seas Health Care, Hull, U.K.) has a nominal label composition (wt %) of 18% EPA and 12% DHA which, in parallel with other "oils," may not be the actually correct figure in some samples (36). In one product, a "reesterified" ω3 polyunsaturated fatty acid (PUFA)-enriched triglyceride (37–39), the concentrations were: EPA 34%; DPA 3.5%; DHA 19.0% (wt/wt% basis). However the distribution of fatty acids on glycerol in such highly enriched triglyceride oils may not follow that expected for natural fish oils. It is widely accepted based on the work of Brockerhoff and others (cited in 16–18) that in fish oils EPA should be primarily in the 2-position, and DHA should be distributed according to a formula: *sn*-1, 0.28x; *sn*-2, 2.06x; *sn*-3, 0.66x, where x = the mole% total of DHA. Table 2 shows a recent analysis of an encapsulated product in which more EPA is found in positions 1 and 3 than in position 2, and the DHA is higher in position 3 than in position 2. For comparison menhaden oil data are included to confirm that DHA should be located primarily in the 2-position. EPA is less specific in distribution. A recent investigation on the hydrolysis of menhaden oil (40) showed that pancreatic lipase would hydrolyze fatty acids of the outer (1 and 3) positions of triglycerides at different rates related to ethylenic bond positions nearest the carboxyl group, but independently of chain length and number of double bonds (Table 3). The fatty acids liberated from glycerol may follow different distribution routes in the body (Fig. 1) and are not necessarily reassembled with the 2-monoglyceride in chylomicrons.

Ethyl esters and free acids. An increasing number of biomedical papers have reported the use of ethyl esters (42–48). These can offer a high concentration of ω3 fatty acids based on urea complexing (35), or urea complexing combined with supercritical CO_2 (49) or chromatographic techniques (50). The hydrolysis of ethyl esters by pancreatic lipase *in vitro* is 10–50 times slower than that of triglycerides (40). This is not the same as *in vivo* hydrolysis by this lipase in the intestinal lumen (41). The possibility of hydrolysis in the intestinal wall after absorption, as shown in Figure 1, is suggested by the preferential incorporation of EPA, administered as ethyl esters, into plasma phospholipids (51). There is a basic difference in the effects of EPA, as acids or esters, on arachidonic acid in human plasma (52).

The normal human diet does not contain much fatty acid in free form. There is, however, considerable lipolytic activity present in humans which affects esters prior to the important intestinal lipolytic activity; lipase is the major enzyme found in human gastric juice (53,54). In piglet stomachs, fish oil was broken down to the extent of 50% to diglyceride and free fatty acids (55). Iverson (56) has shown that there is rapid gastric hydrolysis of seal milk triglycerides in the stomach of nursing grey seal pups, and Puppione *et al.* (34) have suggested more studies on this form of fat absorption and transport. In humans, a feedback mechanism may limit hydrolysis (57), but local absorption of EPA or DHA is still possible. One reference to a beneficial effect of fish oil in the stomach (58) may be pertinent.

There are numerous problems created by the various forms of administration possible for the long-chain ω3 fatty acids in humans. The enriched triglycerides may have abnormal fatty acid distributions on the glycerol backbone and this information is rarely provided. Presumably enzymes are used to add an enriched fatty acid mixture to glycerol (59). Usually the total for EPA and DHA is indicative of one or more such fatty acids per molecule, but as Figure 1 indicates, whether these go to the liver or are circulated as chylomicron triglycerides is an open question. That ethyl esters are fully absorbed is now known (60). It is reported that 6 g of ethyl ester per day is totally absorbed (Horrobin,

TABLE 2

Mole Percent Distribution of Selected Fatty Acids on Glycerol of Efamol Fish Oil[a,b] and of Menhaden Oil[c]

Glycerol position	Fatty acid			
	18:4ω3	20:5ω3	22:5ω3	22:6ω3
Efamol total	4.0	18.0	2.2	10.8
sn-1% in position	4.0	15.0	1.0	2.0
% of total	(33.0)	(27.0)	(11.0)	(5.0)
sn-2% in position	5.0	18.0	4.0	15.0
% of total	(42.0)	(33.0)	(63.0)	(42.0)
sn-3% in position	3.0	21.0	2.0	20.0
% of total	(26.0)	(39.0)	(26.0)	(53.0)
Menhaden total	3.6	16.9	2.3	9.1
sn-1 and *sn*-3	3.6	13.2	1.2	6.6
sn-2	3.7	11.7	2.8	9.8

[a]Adapted from Lawson and Hughes (33).
[b]MaxEPA is stated (33) to be similar.
[c]Adapted from Yang *et al.* (40).

TABLE 3

Percentage of Selected Fatty Acids (mole percent) in Free Fatty Acids and Monoacylglycerols of Rat Lumenal Lipids During Lipolysis of Menhaden Oil Triacylglycerols[a] and from *in vitro* (20%) Lipolysis[b]

Lipid class	Fatty acid			
	18:4ω3	20:5ω3	22:5ω3	22:6ω3
Total in TG[c]	3.6	16.9	2.3	9.1
FFA[d] in lumen	3.6	13.9	1.6	4.8
MG[e] in lumen	3.5	14.6	3.8	18.0
FFA (*in vitro*)	1.4	4.1	0.8	1.7
MG (*in vitro*)	4.4	13.1	3.0	10.8

[a]Adapted from Yang *et al.* (41).
[b]Adapted from Yang *et al.* (40).
[c]TG, triglycerides.
[d]FFA, free fatty acid.
[e]MG, monoglyceride.

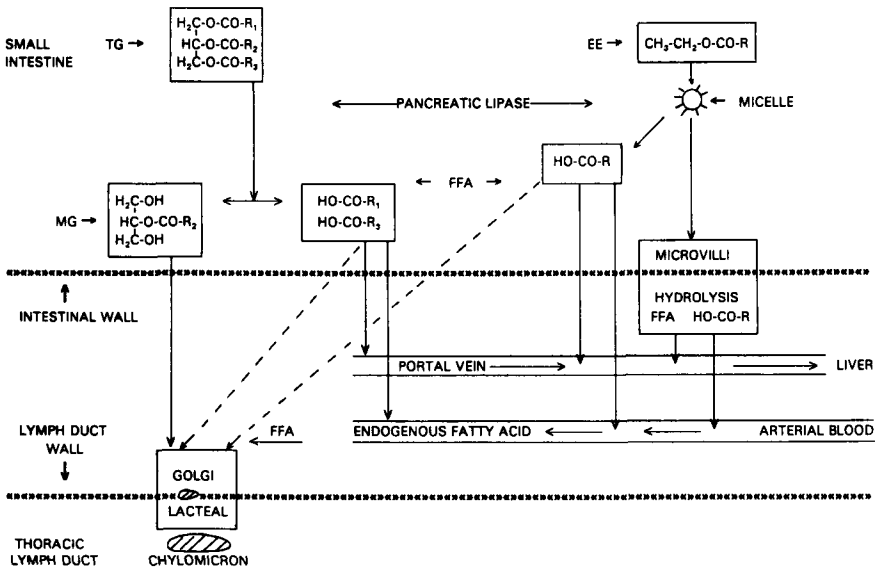

FIG. 1. Some possible origins for fatty acids found in chylomicrons, with special reference to hydrolysis of ethyl esters. The action of pancreatic lipase on ethyl esters *in vivo* and *in vitro* is described elsewhere in detail (40,41).

private communication), and as much as 15 g/day has been administered. Another report on blood pressure suggests that 3 g/day is effective but 6 g/day does not double the clinical effect (45). No ethyl esters have been reported in the blood lipids of humans given highly purified EPA in that form (61), so it is evidently totally hydrolyzed during digestion. Since 60–70% (by weight) concentrates of EPA plus DPA plus DHA are readily prepared, the 6 g/day yields about 4 g/day of the ω3 fatty acids, which, depending on the symptoms, could be a therapeutic dosage (45,62–64). As little as 300 mg/day could be a "preventive" (in cardiovascular terms) dosage (64). Ethyl esters, which are already established encapsulated products in the health supplement market, could in most cases be free from cholesterol and saturated acids (Fig. 2). The possibility of comparing different clinical studies on a dose basis is also clear. This is, at present, often virtually impossible with triglycerides for the reasons given above, but the nonlinear absorption of ethyl esters creates another problem.

Free acids have been reputed to irritate the stomach. This may refer in practice to shorter chain fatty acids, for example butyric acid from rancid butter. Historically, very thorough mastication of foods was practiced at various times, usually with beneficial results (65). Lingual gastric lipase could have been effective, in such cases, in providing all types of free acids for gastric absorption (66). Another report refers to avoiding esophageal irritation through the use of free acids in capsules (33). Since most encapsulated ω3 products are taken with food, there does not seem then to be a serious objection to their use in free acid form beyond some eructation (48). Co-absorption with other fats is well established, and if gastric absorption is rapid, it may explain why the plasma triglyceride input from free acid sometimes follows the triglyceride rise (67) or precedes it (33). Gastric lipases actually produce free acids *in vitro* (54,57), a further indication that free acids are probably well accepted as reported elsewhere (48).

Ethyl esters of ω3 fatty acids could be used for encapsulated supplements or enteral products, but triglycerides are traditional for parenteral nutrition. A new challenge is then to consider whether highly concentrated free acids could be administered in this way, perhaps as salts (68) or absorbed on albumin, or even simply dissolved in the triglycerides already in these products (69). The point is that relative to the total fat only 1 or 2% of long-chain ω3 fatty

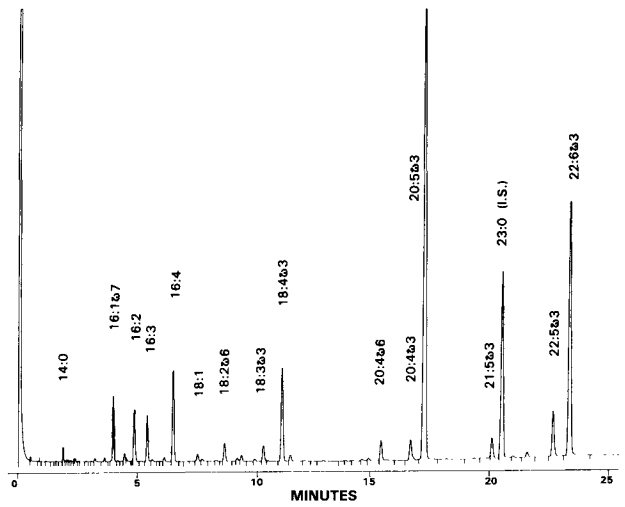

FIG. 2. Gas-liquid chromatographic analysis of a retail fish oil concentrate sold in ethyl ester form, with added ethyl 23:0 internal standard for quantitation. A bonded polyglycol Omegawax-320 flexible fused silica column (Supelco Inc., Bellefonte, PA) (30 × 0.32 mm i.d.) was operated in a Perkin-Elmer model 8420 gas chromatograph (GC, Norwalk, CT). GC oven temperature: 195° for 8 min, program at 3°/min to 240°, hold at 240°.

acids (EPA, DPA, DHA) needs to be supplied if it is in the form of a 60–70% free fatty acid concentrate. Like the ethyl esters, free acid concentrates can be obtained free of saturated acids, cholesterol, etc. Whether the free acids so administered are in any way toxic or are more immediately beneficial compared to triglycerides are some of the questtions to be answered.

Fish. Fatty fish eaten in moderation (30,70), or as a steady diet (71,72), show no obvious side effects. However, fish can be expensive and is not always a popular food in many population groups (73). It is surely important to provide access to fish oil fatty acids for those who do not or cannot eat fish, despite numerous warnings of risks (74), most of which are somewhat hypothetical compared to the real risks and side effects often associated with potent synthetic drugs. In contrast, the long-chain ω3 fatty acids, whether from fish or fish oil concentrates of any type, are purely natural dietary components and part of a system of checks and balances normal in the human body (75,76).

For example fish oil administration to achieve triglyceride reduction (77) may be accompanied by an increase in plasma glucose, which can be offset by increased administration of vitamin E (78). The latest considered opinions of experts (79,80) are that we are still grappling with various aspects of functions of ω3 fatty acids in what are instances of adult-onset degenerative diseases, a rather different problem from that of treating acute disease states. Peculiarly, our understanding of nutritional aspects of longer-chain ω3 fatty acids for early human development is not much further advanced at the other end of our life spans (81,82).

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