Proceedings of the Nutrition Society (1985), **44**, 391–397

Influence of fish-oil supplements on man

By T. A. B. SANDERS, *Department of Nutrition, Queen Elizabeth College, University of London, Campden Hill Road, London W8 7AH*

Cod-liver oil has been used as a household remedy for centuries and over the course of time scientific explanations for its properties have become available. The first extensive clinical tests of cod-liver oil seem to have been made by Samuel Kay, a physician at the Manchester Infirmary from 1752 to 1784. He gave doses of cod-liver oil to patients suffering from bone diseases and rheumatism and wrote 'the good effects of it are so well known among the poorer sort that it is particularly requested by them for almost every lameness'. Cod-liver oil played a central role in the isolation and discovery of vitamins A and D because it was known to cure night blindness, corneal xerosis and rickets. The nutritional value of cod-liver oil was officially acknowledged during World War II by the Ministry of Food who established a scheme for the free distribution of the oil to all infants up to 5 years old and to pregnant and nursing women. The issue of cod-liver oil by the Ministry of Food had a remarkable effect on the sales of the oil after the war. Indeed, the administration of cod-liver oil to children was widespread until the late 1950s. Cod-liver and halibut-liver oils still remain a popular supplementary source of vitamins A and D. There has been renewed interest in fish-oil supplements since Dyerberg *et al.* (1978) postulated that dietary eicosapentaenoic acid (20:5ω3; EPA) may offer protection against acute myocardial infarction by way of its influence on blood lipids, prostaglandins and haemostatic function.

Fish oil is a readily available source of EPA, consequently fish-oil supplements have been used to evaluate the effect of EPA on blood lipids, haemostasis and eicosanoid production. Different fish oils of varying composition and dose have been used so there are difficulties in extrapolating the results from one study to another. It should be emphasized that fish oils do contain other pharmacologically active ingredients apart from EPA. Most fish oils contain significant amounts of other ω3 polyunsaturated fatty acids such as docosahexaenoic acid (22:6ω3; DHA), which shares several of the pharmacological effects of EPA (Corey *et al.* 1983), and so there is no justification in attributing all the effects observed with fish-oil supplements to EPA. The fatty acid composition of fish oil varies considerably from species to species and seasonally (Ackman, 1982) and is dependent on the food chain. As a rule fish oils from cold-water fish contain high proportions of ω3 fatty acids, mainly EPA and DHA with smaller amounts of 18:4ω3 and 22:5ω3. The oils from certain tropical fish contain a relatively high proportion of arachidonic acid (20:4ω6; AA) (O'Dea & Sinclair, 1982).

Generally, fish-liver oils contain high levels of vitamins A and D, the highest concentrations being found in shark- and halibut-liver oil. Oils extracted from the crushed whole fish such as anchovy, sardine and menhaden oil contain far lower

levels of the oil-soluble vitamins. All fish oils contain between 5 and 15% palmitoleic acid (16:1) and certain fish oils, such as mackerel, herring and salmon oils, contain substantial amounts of gadoleic (20:0ω11) and cetoleic (22:1ω11) acids, which are derived from the corresponding fatty alcohols produced by copopods.

C_{20-22} monoenes, like erucic acid (22:1ω9), are initially poorly oxidized and, when fed to experimental animals in large amounts, can lead to a transient myocardial lipidosis (Food and Agriculture Organization/World Health Organization, 1977; Cristopherson *et al.* 1982). Sardine, pilchard, anchovy and menhaden oils are low in C_{20-22} monoenes but contain high levels (25–45%) of saturated fats, in particular myristic (14:0) and palmitic (16:0) acids. Many studies have used an oil blend called MaxEPA (Seven Seas Health Care, Hull) which has a standardized composition of 18% EPA and 12% DHA and is low in C_{20-22} monoenes and vitamins A and D but does contain 25–35% saturated fatty acids. Synthetic antioxidants and vitamin E are also added to MaxEPA in order to guard against lipid peroxidation.

The observation that Greenland Eskimos have the highest recorded intakes of fat (Bang & Dyerberg, 1980) in the world yet have a low incidence of coronary heart disease (Kromann & Green, 1980) has considerably shaken the dietary fat hypothesis that a high intake of animal fat is the primary cause of coronary heart disease. It is uncertain whether this is because fish oil offers protection from atherosclerosis or because it reduces the severity of the complications of atherosclerosis, such as acute myocardial infarction and cerebral thrombosis.

Influence of fish oils on plasma lipids

High levels of low-density lipoprotein (LDL)-cholesterol, and very-low-density lipoprotein (VLDL)-triglycerides coupled with low levels of high-density lipoprotein (HDL)-cholesterol, especially that associated with the HDL_2 fraction, are associated with the development of atherosclerosis (Havel, 1982). Hyperlipidaemia is also associated with high levels of certain clotting factors (Elkeles *et al.* 1980) and increased platelet reactivity (Stuart *et al.* 1980; Zahavi *et al.* 1981). Eskimos living on their traditional seafood diet, which provides approximately 5 g EPA and 6 g DHA/d, have high levels of HDL-cholesterol, moderately low levels of LDL cholesterol and very low levels of VLDL triglycerides compared with Eskimos living on a Western diet (Bang & Dyerberg, 1980). It has been claimed that Eskimos are relatively free from atherosclerosis (Sinclair, 1980) but post-mortem studies on Canadian Eskimos, whose diets consisted of seal meat and fish, report the presence of atherosclerosis although less severe than expected for their age (Schaeffer, 1959).

Fish oils possess a cholesterol-lowering effect (Ahrens *et al.* 1959; Kingsbury *et al.* 1961; Stansby, 1969) that is attributed to their content of ω3 fatty acids and seems to result from a reduction in the proportion of cholesterol associated with both LDL and VLDL (Harris *et al.* 1983). This effect is only noted with high intakes in excess of about 8 g C_{20-22} ω3 fatty acids. LDL turnover studies have

been carried out in subjects consuming in excess of 20 g C_{20-22} ω3 fatty acids and show a fall in the absolute synthetic rate of LDL and a slight fall in fractional catabolic rate (Illingworth *et al.* 1984). This is in contrast to studies with linoleic acid-rich vegetable oils which show an increase in fractional catabolic rate (Shepherd *et al.* 1980; Illingworth *et al.* 1981).

A slight increase in HDL-cholesterol concentration is seen in healthy subjects following the consumption of daily supplements of 20 ml cod-liver or 10–20 g MaxEPA (Sanders *et al.* 1981; Sanders & Hochland, 1983; Sanders & Roshanai, 1983). This increase in HDL-cholesterol appears to be due to an increase in HDL_3-cholesterol (Sanders & Mistry, 1983; T. A. B. Sanders, K. Upton and M. Mistry, unpublished results) rather than the protective HDL_2 fraction. Hepatic enzyme induction (Bolton *et al.* 1980) can increase HDL-cholesterol levels and it is pertinent that DHA induces hepatic monooxygenase (Van Rollins *et al.* 1984). HDL-cholesterol concentrations could also be increased by an increase in the enterohepatic circulation of bile acids.

Fish-oil supplements possess a plasma-triglyceride-lowering effect not shared by vegetable oils rich in either linoleic (18:2ω6) or linolenic (18:3ω3) acids (Sanders *et al.* 1981; Mortensen *et al.* 1983; Sanders & Hochland, 1983; Sanders & Roshanai, 1983) that is manifest at low doses. Sanders & Roshanai (1983) showed that 10 g MaxEPA daily, but not lower doses, had a significant triglyceride-lowering effect in normal subjects. Saynor (1984) and Simons *et al.* (1985), also using MaxEPA, reported a plasma triglyceride-lowering effect in hyperlipidaemic patients with 5 and 6 g/d respectively of MaxEPA. Work with rats using purified ethyl esters has shown that both EPA and DHA possess this triglyceride-lowering effect (G. Kermode and T. A. B. Sanders, unpublished results).

Fish-oil supplements have a triglyceride-lowering effect of sufficient magnitude to be of therapeutic value in patients with primary hypertriglyceridaemia (Sanders & Mistry, 1983; Sanders *et al.* 1985). Hypertriglyceridaemia results from an imbalance between the rate of produced triglyceride and its removal from the blood. An increased rate of clearance of triglyceride from plasma seems an unlikely explanation for the effect since HDL_2-cholesterol concentrations do not increase, neither does the fractional rate of catabolism of VLDL change (Nestel *et al.* 1984; Sanders *et al.* 1985). There is a marked reduction in the absolute synthetic rate of VLDL-triglyceride (Nestel *et al.* 1984; Sanders *et al.* 1985) in hypertriglyceridaemic patients with fish-oil supplementation so the mechanism for this effect on triglyceride appears to be a decreased rate of hepatic triglyceride synthesis. A reduction in VLDL synthesis would in turn accelerate chylomicron clearance as a similar mechanism clears both VLDL and triglycerides from blood.

Influence of fish oils on membrane lipids

It is possible to cause substantial changes in polyunsaturated fatty acid composition of membrane phospholipids with fish-oil supplements (Sanders *et al.* 1981). The extent to which it is possible to modify platelet membrane composition with different types of ω3 fatty acids was studied by Sanders & Younger (1981).

https://doi.org/10.1079/PNS19850064 Published online by Cambridge University Press

Linseed-oil supplements providing 6·5 g linolenic acid taken daily for 2 weeks by healthy volunteers only led to a very small increase in the proportion of EPA but no change in that of 20:4ω6 in platelet lipids. In contrast, 2·5 g preformed EPA/d as fish-oil concentrate (MaxEPA) led to a large increase in the proportion of EPA and a decrease in that of 20:4ω6 in platelet lipids. Even intakes as low as 1 g EPA/d lead to a significant increase in the level of EPA in platelet phospholipids (Sanders & Roshanai, 1983). Changes in platelet lipid composition occur rapidly, usually within 1 week. So far no study using fish-oil supplements has produced changes in platelet lipid composition of the scale seen in Greenland Eskimos. This may be because the dietary intakes and body stores of linoleic acid of the experimental subjects are relatively high compared with Eskimos.

It is uncertain to what extent membrane composition must be altered in order to affect function. It has been suggested that it may be necessary to modify the fatty acid composition of specific lipid pools (Weiner & Sprecher, 1984), in particular that of phosphatidyl inositol (PI), in order to alter eicosanoid production. Fish-oil supplements do not appear markedly to alter the fatty acid composition of platelet PI: the changes that take place are mainly in the phosphatidyl ethanolamine and phosphatidyl choline fractions (Brox *et al.* 1981; Fischer & Weber, 1983; Ahmed & Holub, 1984). Cod-liver oil supplementation in addition leads to an increase in lignoceric acid (24:1) and a decrease in behenic acid (22:0) in platelet sphingomyelin (Ahmed & Holub, 1984). Changes in membrane composition, besides influencing eicosanoid formation, may also influence membrane fluidity.

Influence of fish oils on eicosanoid production

As a general rule, the cyclo-oxygenase and lipoxygenase products of EPA are either inactive or less active compared with those derived from arachidonate. This led to the postulate that the replacement of AA with EPA would modulate the production of active eicosanoids (Moncada & Vane, 1979). There has, however, been considerable controversy as to whether prostaglandins and leukotrienes are formed from EPA in vivo. EPA is a poor substrate for platelet cyclo-oxygenase but is a good substrate, compared with AA, for the lipoxygenase (Gryglewski *et al.* 1979; Needleman *et al.* 1979; Hamberg, 1980) and so only small quantities of thromboxane B_3 are formed (Fischer & Weber, 1984). Although the prostaglandin PGI_3 is not formed in rats given fish oils (Hornstra *et al.* 1981), its urinary metabolite has been detected by gas chromatography and mass spectroscopy in subjects given 40 ml cod-liver oil daily for 1 week (Fischer & Weber, 1983). Prescott (1984) has shown that leukotriene B_5 is formed in volunteers following the consumption of 40 ml MaxEPA/d for 3 weeks. However, it remains to be shown whether these eicosanoids are formed in sufficient amounts to be of physiological significance.

The predominant effects of EPA and DHA on eicosanoid production are probably as inhibitors of linoleic acid and AA metabolism: they readily displace AA from membrane lipids and inhibit the conversion of linoleic acid to AA (Brenner & Peluffo, 1967) and are competitive inhibitors for cyclo-oxygenase (Lands *et al.*

1973; Hamberg, 1980; Corey *et al.* 1983). DHA is the major polyunsaturated fatty acid in some tissues such as the brain and there is a possibility that it plays an important role in down-regulating prostaglandin production in these tissues. Both EPA and DHA are potent inhibitors of human platelet aggregation in vitro (Gryglewski *et al.* 1979; T. A. B. Sanders and A. M. Lilburne, unpublished results) and several studies have noted a reduction in platelet thromboxane B_2 formation stimulated by collagen following the administration of fish-oil supplements (Brox *et al.* 1981; Fischer & Weber, 1983; Sanders & Hochland, 1983). Knapp & Fitzgerald (1984) found a marked reduction in serum thromboxane B_2 (>90%) but no change in the urinary metabolite of prostacyclin (PGI_2) with 40 ml MaxEPA daily for 4 weeks. This implies that fish oil selectively decreases the formation of thromboxane A_2 from AA in man.

Prolongation of bleeding time

Template bleeding time is prolonged by daily supplements of 20 ml cod-liver-oil or MaxEPA-oil supplements (Sanders *et al.* 1980; Sanders & Roshanai, 1983; Saynor *et al.* 1984). This is not accompanied by any change in the levels of clotting factors (Sanders *et al.* 1981) or by any marked inhibition of platelet aggregation induced by collagen or ADP (Goodnight *et al.* 1981; Sanders *et al.* 1981; Sanders & Roshanai, 1983). However, a slight increase in the threshold dose of collagen to result in aggregation has been noted (Brox *et al.* 1981; Hirai *et al.* 1982; Sanders & Hochland, 1983). Moreover, reductions in β-thromboglobulin and platelet factor 4, which are indicators of in vivo platelet aggregation, have been reported following the consumption of 20 ml MaxEPA daily (Hay *et al.* 1982). It seems that the primary role of thromboxane A_2 is to cause vasoconstriction (Butler *et al.* 1982). Consequently the prolongation of bleeding time observed when fish oil is given could be a result of a decreased vasoconstrictor response to injury rather than impaired platelet plug formation. Thorngren (1983) argues against this because she was unable to demonstrate a reduction in the concentration of thromboxane B_2 in blood emerging from bleeding time incisions of subjects with prolonged bleeding times following fish consumption. A reduction in whole-blood viscosity and an increase in erythrocyte deformability have been reported in individuals with low intakes of fish oil (Terano *et al.* 1983; Woodcock *et al.* 1984). The prolongation of template bleeding time represents an attenuated response to vascular injury. An attenuated response might mitigate the complications of atherosclerosis; indeed, studies with experimental animals (Black *et al.* 1979; Culp *et al.* 1980) have shown that fish-oil supplementation limits tissue damage following experimentally-induced ischaemia.

Conclusion

Moderate intakes of fish oil, providing 3–5 g C_{20-22} ω3 fatty acids/d (provided by 150–200 g oily fish), markedly lowered VLDL-triglyceride concentrations in plasma and led to a slight prolongation of template bleeding time. It remains to be shown whether the consumption of modest amounts of fish-oil supplements has any beneficial effects on morbidity and mortality from cardiovascular disease.

REFERENCES

Ackman, R. G. (1982). In *Nutritional Evaluation of Long-chain Fatty Acids in Fish Oil*, pp. 25–88 [S. M. Barlow and M. E. Stansby, editors]. London: Academic Press.
Ahmed, A. A. & Holub, B. J. (1984). *Lipids* **19**, 617–624.
Ahrens, E. H., Insull, W., Hirsh, J., Stoffel, W., Peterson, M. L. & Farquar, J. W. (1959). *Lancet* **i**, 115–116.
Bang, H. O. & Dyerberg J. (1980). In *Advances in Nutrition Research*, vol. 3, pp. 1–22 [H. H. Draper, editor]. New York: Plenum Press.
Black, K. L., Culp, B., Madison, D., Randall, O. S. & Lands, W. E. M. (1979). *Prostaglandins and Medicine* **5**, 257–268.
Bolton, C. H., Jackson, L., Roberts, C. J. C. & Hartog, M. (1980). *Clinical Science* **58**, 419–421.
Brenner, R. R. & Peluffo, R. O. (1967). *Biochimica et Biophysica Acta* **137**, 184–186.
Brox, J. H., Kille, J. E., Gunnes, S. & Nordoy, A. (1981). *Thrombosis and Haemostasis (Stuttgart)* **46**, 604–611.
Butler, K. D., Maguire, E. D., Smith, J. R., Turnbull, A. A., Wallis, R. B. & White, A. M. (1982). *Thrombosis and Haemostasis (Stuttgart)* **47**, 46–82.
Corey, E. J., Shih, C. & Cashman, J. R. (1983). *Proceedings of the National Academy of Sciences, USA* **80**, 3581–3584.
Cristopherson B. O., Norseth, J., Thomassen, M. S., Christiansen, E. N., Norum, K. R., Osmundsen, H. & Bremer, J. (1982). In *Nutritional Evaluation of Long-chain Fatty Acids in Fish Oil*, pp. 89–140 [S. M. Barlow and M. E. Stansby, editors]. New York: Academic Press.
Culp, B. R., Lands, W. E. M., Lucches, B. R., Pitt, R. & Romson, J. (1980). *Prostaglandins* **20**, 1021–1031.
Dyerberg, J., Bang, H. O., Stofferson, E., Moncada, S. & Vane J. R. (1978). *Lancet* **i**, 117–119.
Elkeles, R. S., Chakrabarti, R., Vickers, M., Stirling, Y. & Meade, T. W. (1980). *British Medical Journal* **281**, 973.
Fischer, S. & Weber, P. C. (1983). *Biochemical Biophysical Research Communications* **116**, 1091–1099.
Fischer, S. & Weber, P. C. (1984). *Nature* **307**, 165–168.
Food and Agriculture Organization/World Health Organization. (1977). *Dietary Fats and Oils in Human Nutrition, A Joint FAO/WHO Report*, Rome: FAO.
Goodnight, S. H., Harris, W. S. & Connor, W. E. (1981). *Blood* **58**, 880–885.
Gryglewski, R. J., Salmon, J. A., Ubatuba, F. B., Weatherley, B. C., Moncada, S. & Vane J. R. (1979). *Prostaglandins* **18**, 453–478.
Hamberg, M. (1980). *Biochimica et Biophysica Acta* **618**, 389–398.
Harris, W. S., Connor, W. E. & McMurry, M. P. (1983). *Metabolism* **32**, 179–184.
Havel, R. J. (editor) (1982). *Lipid Disorders. The Medical Clinics of North America*, vol. 66. London: W. B. Saunders Co.
Hay, C. R. M., Durber, A. P. & Saynor, R. (1982). *Lancet* **i**, 1269–1272.
Hirai, A., Terano, T., Hamazaki, T., Sajiki, J., Kondon, S., Ozawa, A., Fujita, T., Miyamoto, T., Tamura, Y. & Kumagai, A. (1982). *Thrombosis Research* **28**, 285–298.
Hornstra, G., Christ-Hazelhof, E., Haddeman, E., ten Hoor, F. & Nugteren, D. H. (1981). *Prostaglandins* **21**, 727–736.
Illingworth, D. R., Harris, W. S. & Connor, W. E. (1984). *Arteriosclerosis* **4**, 270–275.
Illingworth, D. R., Sundberg, E. E., Becker, N., Connor, W. E. & Alaupovic, P. (1981). *Arteriosclerosis* **1**, 380.
Kingsbury, K. J., Aylott, C., Morgan, D. M. & Emmerson, R. (1961). *Lancet* **i**, 739–741.
Knapp, H. R. & Fitzgerald, G. A. (1984). *Symposium on n-3 Fatty Acids*, July 1984, University of Reading. Potters Bar: International Association of Fishmeal Manufacturers.
Kromann, N. & Green, A. (1980). *Acta Medica Scandinavica* **208**, 401–406.
Lands, W. E. M., LeTellier, P. R., Rome, L. H. & Vanderhoek, J. Y. (1973). *Advances in Bioscience* **9**, 15–28.
Moncada, S. & Vane, J. R. (1979). *New England Journal of Medicine* **300**, 1142–1147.
Mortensen, J. Z., Schmidt, E. B., Nielsen, A. H. & Dyerberg, J. (1983). *Thrombosis and Haemostasis (Stuttgart)* **50**, 543–546.

Needleman, P., Raz, A., Minkes, M. S, Ferrendelli, J. A. & Sprecher, H. A. (1979). *Proceedings of the National Academy of Sciences, USA* **76,** 944–948.
Nestel, P. J., Connor, W. E., Reardon, M. F., Connot, S., Wong, S. & Boston, R. (1984). *Journal of Clinical Investigation* **74,** 82–89.
O'Dea, K. & Sinclair, A. J. (1982). *American Journal of Clinical Nutrition* **36,** 868–872.
Prescott, S. M. (1984). *Symposium on n-3 Fatty Acids*, July 1984, University of Reading. Potters Bar: International Association of Fishmeal Manufacturers.
Sanders, T. A. B. & Hochland, M. (1983). *British Journal of Nutrition* **50,** 521–529.
Sanders, T. A. B. & Mistry, M. (1983). *British Journal of Clinical Practice* **31,** Suppl., 78–81.
Sanders, T. A. B., Naismith, D. J., Haines, A. P. & Vickers, M. (1980). *Lancet* **ii,** 1189.
Sanders, T. A. B. & Roshanai, F. (1983). *Clinical Science* **64,** 91–99.
Sanders, T. A. B., Sullivan, D. R., Reeve, J. & Thompson, G. R. (1985). *Arteriosclerosis* **5,** (In the Press).
Sanders, T. A. B., Vickers, M. & Haines, A. P. (1981). *Clinical Science* **61,** 317–324.
Sanders, T. A. B. & Younger, K. M. (1981). *British Journal of Nutrition* **45,** 613–616.
Saynor, R. (1984). *Lancet* **ii,** 696.
Saynor, R., Verel, D. & Gillot, T. (1984). *Atherosclerosis* **50,** 3–10.
Schaeffer, O. (1959). *Canadian Medical Journal* **81,** 386–393.
Shepherd, J., Packard, C. J., Grundy, S. M., Yeshurum, D., Gotto, A. M. & Taunton, O. (1980). *Journal of Lipid Research* **21,** 91–99.
Simons, L. A., Hickie, J. B. & Balasubramaniam, S. (1985). *Atherosclerosis* **54,** 75–88.
Sinclair, H. M. (1980). In *Drugs Affecting Lipid Metabolism*, pp. 363–370 [R. Fumigalli, D. Kritchevsky and R. Paoletti, editors]. Amsterdam: Elsevier.
Stansby, M. E. (1969). *World Reveiw of Nutrition and Dietetics* **11,** 46–405.
Stuart, M. J., Gerrard, J. M. & White, J. G. (1980). *New England Journal of Medicine* **302,** 6–10.
Terano, T. Hirai, A., Hamazaki, T., Kobayashi, S., Fujita, T., Tamura, Y. & Kumagai, A. L. (1983). *Atherosclerosis* **46,** 321–331.
Thorngren, M. (1983). Dietary fish and haemostasis. Indications of antithrombotic properties. MD Thesis, University of Lund.
Van Rollins, M., Baker, R. C., Sprecher, H. W. & Murphy, R. C. (1984). *Journal of Biological Chemistry* **259,** 5776–5783.
Weiner, T. W. & Sprecher, H. (1984). *Biochimica et Biophysica Acta* **792,** 293–303.
Woodcock, B. E., Smith, E., Lambert, W. H., Morris Jones, W., Galloway, J. H., Greaves, M. & Preston, F. E. (1984). *British Medical Journal* **288,** 592–594.
Zahavi, J., Betteridge, J. D., Jones, N. A. G., Galton, D. J. & Kakkar, V. V. (1981). *American Journal of Medicine* **70,** 59–64.

Printed in Great Britain