Health effects of fish, fish oils

The dietary implications of fish and fish oil consumption were the focus of two recent international meetings. In Part 1 of this report, Bruce Holub, professor in the Department of Nutritional Sciences at the University of Guelph, Guelph, Ontario, Canada, summarizes highlights from the International Conference on Health Effects of Fish and Fish Oils, held July 30-Aug. 2, 1988, in St. John's, Newfoundland, Canada. In Part 2, J. Edward Hunter of The Procter & Gamble Co. gives highlights from a NATO Advanced Research Workshop held in Italy June 20-23, 1988. Hunter is Associate Editor for JAOCS *News for Health and Nutrition.*

Part 1

The International Conference on Health Effects of Fish and Fish Oils held in Newfoundland addressed recent advances in research directed toward the potential health benefits and clinical applications of omega-3 fatty acids as found in fish and fish oils. The meeting included 34 lectures and 12 poster presentations, as well as an informative panel discussion and public forum. The scientific sessions attracted approximately 150 delegates representing academic institutions, government agencies, and pharmaceutical and food companies from several countries.

Ranjit Chandra of the Memorial University of Newfoundland, organizing chairman, introduced the sessions by pointing out the undesirable side-effects of many conventional drugs now used in clinical practice. He suggested the intake of omega-3 fatty acids as found in fish and fish oils may offer alternative and perhaps safer approaches in the prevention and treatment of certain diseases.

W.E.M. Lands of the Department of Biochemistry, University of Illinois at Chicago, explained why omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fish and fish oils may provide potential nutritional and medical applications. Accelerated rates of eicosanoid (prostaglandins and leukotrienes) biosynthesis from arachidonic acid (AA), the omega-6 fatty acid, are associated with multiple pathophysiological states. The ingestion of omega-3 fatty acid can act antagonistically to the omega-6 and diminish the formation of the AA-derived prostaglandins and leukotrienes.

Joyce Beare-Rogers of Health and Welfare Canada emphasized the involvement of metabolic regulation in the conversion of vegetable oil-derived alpha-linolenic acid to higher omega-3 fatty acids. She also recommended that caution be exerted when using EPA/DHA capsules in certain clinical applications such as in Type II diabetes. The potential nutritional importance of selenium and sulfur-containing amino acids in fish also was raised.

John Kinsella of Cornell University elaborated on the effects of omega-3 fatty acids on the physical properties and function of cellular membranes. Enzyme activities such as 5′-nucleotidase and Ca/Mg-ATPase can be altered by dietary fish oil consumption. DHA may have different effects than EPA in this regard. G. Herzberg of Memorial University delineated the metabolic basis for the plasma triglyceride-lowering effect of dietary fish oil. He concluded that decreased hepatic synthesis and secretion as well as increased removal of triglyceride by muscle lipoprotein lipase activity may contribute to this effect. S. Cunnane of the University of Toronto suggested that triglyceride molecules in liver containing EPA may be hydrolyzed more readily than those containing AA or DHA.

Bruce Holub of the University of Guelph presented data showing that EPA is not randomly incorporated into the individual phospholipid pools in the circulating platelets of volunteers consuming a concentrate of EPA plus DHA. EPA is almost completely excluded from platelet phosphatidylinositol in vivo. It accumulates to a considerable extent in the ether-containing ethanolamine phospholipid (1-alkenyl 2-acyl species) and the diacyl species of the choline phospholipid. Interrelationships between the metabolism and function of the ether phospholipids in mammalian cells and dietary fish oil may have significance in certain pathophysiological states.

Michael Crawford of Nuffield Laboratories of Comparative Medicine provided a historical perspective on the availability of n-3 fatty acids in the food chain in relation to the availability of DHA for brain functions. H. Leaver of the University of Edinburgh presented findings with rats showing that high levels of omega-3 fatty acids in fish oil can prolong gestation and impair parturition. K. Fujimoto of Tohoku University, Japan, reported that rats subjected to Y-maze discrimination tests responded much better when receiving DHA-enriched diets as compared with safflower/olive oil-fed rats, with the DHA content of the brain phospholipid almost twice as high as that for the control group.

A number of presentations highlighted the results of clinical trials using omega-3 fatty acids derived from fish oil. In a double-blind angina study, R. Saynor of Northern General Hospital in Sheffield, England, observed that patients with heart disease exhibited an improvement in exercise tolerance, less dependency on glyceryl trinitrate and a significant decrease in serum triglycerides when given omega-3 supplementation. Decreases in blood viscosity, as well as increases in HDL-cholesterol levels, also were observed in some trials. The potential for certain dosing regimens of omega-3 fatty acids to inhibit the rate of restenosis in patients following coronary angioplasty also was discussed. It was suggested that the inclusion of omega-3 fatty acids in the diet of individuals without coronary heart disease may have a protective and beneficial effect.

B. Weiner of the University of Massachusetts in Worcester provided results from a hyperlipidemic swine model that indicated a marked inhibition of atherosclerosis with dietary fish oil relative to controls. Interestingly, the protective effect occurred even though there was no change in plasma lipid levels. Evidence suggesting beneficial effects of omega-3 fatty acids in some patients with established atherosclerosis also was discussed.

W. Clark of the University of Western Ontario reviewed his work and that of others for the potential benefits of fish oil therapy in kidney disorders. Animal models have indicated the potential for fish oil to delay the onset of nephritis and to reverse proteinuria. Prevention of nephrotoxicity and reversal of the dyslipidemia from cyclosporine with fish oil has been observed. Promising results have been indicated in intervention trials with fish oils in human lupus nephritis and IgA nephritis.

K.K. Carroll of the University of Western Ontario outlined research conducted on fish oils and cancer. Animal models have indicated that high levels of dietary fish oil do not promote and may inhibit development of experimental tumors of the mammary gland, colon and pancreas. However, dietary marine lipids probably have less impact on cancer than on heart disease or other chronic diseases.

J.M. Kremer of Albany Medical College presented data from a clinical trial confirming his earlier observations of beneficial responses in patients with rheumatoid arthritis who ingested a fish oil supplement. Decreases in the number of tender and swollen joints were observed and physician evaluation of pain and global arthritis activity also improved significantly. V. Ziboh of the University of California at Davis and colleagues found moderate improvement of the skin lesions of psoriatic patients given oral supplements of EPA. He correlated these effects to a reduced formation of AA-derived lipoxygenase products. Dietary manipulation was suggested as a possible less-toxic alternative to clinical management of cutaneous inflammatory skin disorders.

Robert Ackman of the Technical University of Nova Scotia discussed the differences between various fish and marine oils in terms of their fatty acid profiles, positional placement of esterified fatty acids and bioavailability. Artemis Simopoulos of the ILSI Research Foundation summarized recent studies on omega-3 fatty acids. She noted depression in the level of an atherogenic protein in plasma with EPA and the possible lesser atherogenic potential of low-density lipoprotein derived from fish oil consumers.

Other stimulating oral presentations and posters contributed to a very rewarding conference.

Part 2

Approximately 120 scientists from 15 countries participated in the NATO Advanced Research Workshop on "Dietary Omega-3 and Omega-6 Fatty Acids: Biological Effects and Nutritional Essentiality," held June 20–23, 1988, in Belgirate, Italy. In addition to NATO, the workshop was sponsored by the International Life Sciences Institute (ILSI) Research Foundation, Division of Nutritional Sciences; ILSI Europe; and the Nutritional Foundation of Italy.

Scientific directors of the workshop were Claudio Galli of the Institute of Pharmacological Sciences, Universitá degli Studi, Milan, Italy, and Artemis Simopoulos of the ILSI Research Foundation, Division of Nutritional Sciences, Washington, D.C. The program consisted of both plenary and poster presentations discussing dietary sources of omega-3 and omega-6 fatty acids; their chemistry, biosynthesis and interactions; and their biological effects, including their role in development, cell activation processes and human diseases.

Dietary sources

K. Bloch of Harvard University reviewed early studies involving the alga *Euglena gracilis* which demonstrated that the formation of α-linolenic acid from linoleic acid by chloroplasts increased as photosynthetic efficiency increased (e.g., higher CO_2 concentration and/or higher light intensity). Michael Crawford of Nuffield Laboratories of Comparative Medicine, London, noted that the marine food chain is rich in long chain omega-3 fatty acids—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—and that the land food chain is rich in the shorter chain omega-6 fatty acid linoleic acid. In view of the requirement for DHA for brain function and considering man's relatively large brain size (as a percentage of body weight) compared with that of many land-based mammals, Crawford suggested that man probably evolved near a marine environment rather than on land.

Discussing dietary aspects of omega-3 fatty acids, Joyce Beare-Rogers of Health and Welfare Canada commented that α-linolenic acid provides the only source of omega-3 fatty acids for vegetarians and is converted to EPA and DHA in individuals consuming little seafood or organ meats. However, she noted, feeding α-linolenic acid to cynomolgus monkeys resulted in conversion to EPA and DHA (in erythrocytes) at a slower rate and to a lesser extent than feeding EPA and DHA (in fish oil) to bypass the desaturation and elongation steps.

O. Adams of the University of Munich used world production data on edible fats and oils to estimate average intakes of linoleic acid at 10 g/person/day and α-linolenic acid at 1 g/person/day (linoleic/linolenic acid ratio of 10).

Using production data on salad and cooking oil, salad dressing, margarine, shortening and food service fats and oils, J. Edward Hunter of The Procter & Gamble Co. estimated that per capita availability of α-linolenic acid from vegetable oil products is about 1.2 g/person/day in the U.S. and about 2 g/person/day in Canada. Considering U.S. Department of Agriculture (USDA) estimates of availability of linoleic acid and reasonable contributions to dietary α-linolenic acid of other foods such as nuts, dairy products and vegetables, Hunter suggested a total dietary ratio of linoleic to linolenic acid of about 10, essentially in agreement with the estimate of Adam.

H.J. Wille of Nestlé Research Center discussed processing steps currently used to produce fish oil for dietary applications.

Chemistry, biosynthesis and interactions

Reviewing omega-3 and omega-6 fatty acid metabolism, H.W. Sprecher of Ohio State University noted that uncertainty remains as to why membrane lipids generally contain large amounts of linoleate and arachidonate but only relatively low levels of other omega-6 fatty acids, and also, why α-linolenic acid is not incorporated into membrane lipids even when added to the diet.

B.J. Holub of the University of Guelph reported on a preliminary study indicating that feeding human subjects a canola oil-enriched diet for 25 days resulted in a three-fold increase in EPA in a specific class of platelet phospholipids (1-alkenyl-2-acylphosphatidyl ethanolamine), compared to feeding a sunflowerseed oil-enriched diet. Previous work by Renaud et al. reporting conversion of dietary α-linolenic acid to EPA in platelet phospholipids focused only on total platelet phospholipids rather than on specific phospholipid classes (*American Journal of Clincial Nutrition,* Vol. 43, p. 136, 1986).

In vitro studies by M. Lagarde of the I.N.S.E.R.M. Unit in Villeurbanne, France, have indicated DHA is more potent than EPA in inhibiting platelet functions. P. Budkowski of The Hebrew University of Jerusalem, Rehovot, Israel, emphasized the importance of dietary α-linolenic acid in helping to control the metabolism of arachidonic acid synthesis and thus to reduce the tendency for platelet aggregation.

W. Becker of the National Food Administration, Uppsula, Sweden, reported that based on autoradiographic studies, administration of DHA to man and rats does not lead to accumulation of DHA. Apparently, there is some retroconversion of DHA to EPA by both species.

Role in development

It is now generally recognized that dietary DHA is needed for proper development of the brain and central nervous system in young children. M. Martinez of the Hospital Infantil Valle de Hebron, Barcelona, warned against use of an omega-6/omega-3 unbalanced diet (e.g., high doses of linoleic acid given intravenously), especially for premature infants. This can result in lower-than-normal levels of DHA and increased amounts of linoleic acid in the central nervous system, which could adversely affect development of the child.

S. Innis of the University of British Columbia, Vancouver, reported that among the Canadian Arctic Inuit, who live on Boughton Island and whose major source of dietary fat is marine mammal flesh (largely ringed seal), breast milk has significantly higher levels of EPA and DHA compared to that from Vancouver controls.

A presentation by M. Neuringer of the Oregon Health Sciences University, Beaverton, supported the essentiality of dietary α-linolenic acid for rhesus monkeys for proper development of the brain and retina. She noted that repletion of 10-

month-old omega-3 deficient monkeys with max-EPA restored brain levels of DHA but did not restore visual function. It would be of interest to determine if the impaired visual function might be restored if EPA supplementation began earlier in life, for instance, at three or four months of age.

Studies with young rats by J.M. Bourre of the I.N.S.E.R.M. Unit in Paris have indicated that feeding a diet low in α-linolenic acid causes anomalies in the composition of brain membranes which results in reduced learning ability. Bourre suggested that the minimum requirements for brain development for the rat (0.4% of calories as α-linolenic acid and 2.4% of calories as linoleic acid) may be similar to the requirements for humans.

According to S. Carlson of the University of Tennessee in Memphis, premature human infants may be at risk for inadequate accumulation of DHA in the brain and retina due to the fact that premature birth prevents the normal accumulation of DHA in the brain and liver that occurs during the last trimester of pregnancy. The absence of a source of DHA in the diet and poor ability to convert α-linolenic acid to DHA may predispose the premature infant to subtle changes in visual function and possibly impair learning ability. DHA is found in human milk. Fish oil supplementation of infant formula as well as human milk feeding of premature infants appear to maintain DHA levels of red blood cell membrane phospholipids. However, currently it is uncertain whether dietary DHA may be as important to human infants for development of visual acuity and cognitive learning as it apparently is to rats and monkeys. Studies are under way to examine if the biochemical deficiency of DHA could lead to impaired visual function and subtle changes in the learning behavior of premature infants.

Two international conferences on fish oils draw representatives from government, academia and industry. In the bottom photo, Joyce Beare-Rogers, Ranjit Chandra (organizing chairman), Ken Carroll and Roy Carr participate in the International Conference on Health Effects of Fish and Fish Oils held in Newfoundland. Young Yeo (top photo) of Kyungpook National University answers questions during the meeting's poster session.

Cell activation

C. Galli of the Universitá degli Studi, Milan, presented data indicating that complex interactions and displacements of omega-3 and omega-6 fatty acids take place in plasma and cellular lipids after dietary manipulations and that early steps of cell activation, such as generation of inositol phosphates, are induced by dietary fatty acids.

Cell culture studies by A.A. Spector and coworkers at the University of Iowa suggest that because linoleic acid and omega-3 polyunsaturates can reduce release of prostacyclin by endothelial cells, the type of polyunsaturated fat available in the diet may modulate actions of endothelium that are mediated by eicosanoids.

Discussing the question of whether linoleic acid has functions not fulfilled by α-linolenic acid, W.M.F. Leat of Trinity College, Cambridge, United Kingdom, noted that dietary linoleic acid (but not α-linolenic acid) is essential for parturition in female rats and for proper testicular growth and function in male rats.

Role in human diseases

K.S. Bjerve of the University of Trondheim, Trondheim, Norway, has identified eight adults and one child as having omega-3 fatty acid deficiency, characterized largely by skin atrophy with dandruff-like dermatitis in the adults and growth failure in the child. The symptoms of all the patients improved rapidly after supplementation with α-linolenic acid alone or with a combination of α-linolenic acid and fish oil. These results demonstrate the essentiality of omega-3 fatty acids for humans for normal growth and cell function. Bjerve estimated optimal intakes of 800–1000 mg/day of α-linolenic acid and 300–400 mg/day of very long chain omega-3 fatty acids.

Discussing effects of omega-3 fatty acids on blood lipoproteins, T.A.B. Sanders of the University of London noted that moderate intakes of fish oil concentrates (e.g., 15 g/day) or oily fish providing 3–5 g/day of omega-3 fatty acids do not lower and tend to increase LDL cholesterol levels and thus are not useful for the treatment of hypercholesterolemia. Moderate levels of fish oil, however, do offer a safe and effective means of treatment of hypertriglyceridemia because they reduce the synthesis of hepatic triglycerides. For this reason, Sanders indicated that fish oil supplementation is the preferred treatment in England to control hypertriglyceridemia. α-Linolenic acid at comparable dosages, however, does not lower blood triglycerides.

Beare-Rogers cautioned against indiscriminant use of fish oil by certain patients because a recent report (Ensinck, *JAOCS 65*:509, 1988) noted that supplementation with 8 g of omega-3 fatty acids daily for eight weeks for noninsulin-dependent diabetics improved hypertriglyceridemia but increased fasting plasma glucose levels, thus possibly impairing glucose homeostasis.

In contrast to recent work in the U.S. suggesting that dietary stearic acid may be hypocholesterolemic, S. Renaud of the I.N.S.E.R.M. Unit in Bron, France, commented that risk of thrombosis increases with increasing saturated fat, and particularly stearic acid, intake. In human trials conducted by Renaud and colleagues, the principal effect of dietary α-linolenic acid has been to reduce platelet aggregation (thus possibly decreasing heart attack risk by reducing clotting tendency), whereas the principal effect of increasing dietary linoleic acid has been to reduce blood cholesterol. Renaud said western diets generally should contain more α-linolenic acid and less saturated fat.

D. Kromhout of the University of Leiden, The Netherlands, suggested that the inverse relation between fish consumption (about 30 g/day) and coronary heart disease (*New Engl. J. Med. 312*:1205, 1985) may be explained by reduced serum total and IDL triglyceride levels seen in subjects consuming about 30 g of fish per day compared to subjects consuming about 2 g of fish per day. This hypothesis currently is being tested in an intervention trial involving addition of 1 g of omega-3 (or 1 g of omega-6) fatty acids per day to the diet of men age 30–60 who do not eat fish during the intervention period.

H.R. Knapp of Vanderbilt University added that a high dose of fish oil (50 ml/day for one month) lowered diastolic blood pressure in a group of human subjects (mechanism unknown), whereas comparable amounts of safflower oil had no effect.

In the skin, linoleic acid is a constituent of stratum corneum ceramides which may play an important role in preventing transepidermal water loss. H.S. Hansen of the Royal Danish School of Pharmacy, Copenhagen, reported that dietary arachidonic acid can prevent the transepidermal water loss seen in EFA-deficient rats, but it is linoleic acid which is found in the epidermal ceramides of the arachidonic acid-supplemented rats, indicating that dietary arachidonic acid can be retroconverted to linoleate by EFA-deficient rats. This suggests that at least in rats, linoleic acid has an essential function of its own without being converted to arachidonic acid.

J.M. Kremer of Albany Medical College reported observations of dose-dependent clinical improvements along with alterations of immunological parameters in a group of 49 rheumatoid arthritis patients given a supplement of EPA and DHA for 24 weeks. Kremer commented that fish oil supplements may have an advantage over drugs commonly available for arthritis in that the drugs often produce toxic effects that have not been seen to date with the fish oil treatments.

In the area of cancer, R.A. Karmali of Rutgers University reviewed recent animal studies indicating that diets high in fish oil and adequate in essential fatty acids seem to inhibit tumor growth and metastasis, with few exceptions. On the other hand, the "protective" effect of fish oil has been reported only at high dietary levels (above 10% by weight). One result of feeding high levels of EPA to rats has been inhibition of expression of the oncogene H-rats in mammary explants exposed to carcinogens such as dimethylbenz(a)anthracene (DMBA). This may be a mechanism by which high dietary levels of fish oil inhibit the promotion of DMBA-induced mammary tumors.

On a more controversial note, D.F. Horrobin of Efamol Research Institute, Kentville, Nova Scotia, said evening primrose oil (75% linoleic acid, 9% γ-linolenic acid) is effective in treating such conditions as atopic eczema, rheumatoid arthritis, and diabetic neuropathy, the benefits being attributed to the γ-linolenic acid present in the oil. Questions were raised, however, about the validity of the studies discussed by Horrobin because they were not properly controlled for intake of linoleic acid. Placebos for these studies consisted either of paraffin, which lacks linoleic acid, or olive oil, which contains low levels of linoleic acid compared with evening primrose oil.

Summary and conclusions

At a round-table discussion, it was generally agreed that both linoleic acid and α-linolenic acid are essential for humans and that some increase in the intake of omega-3 fatty acids (both α-linoleic acid, as well as the longer chain EPA and DHA), compared with current levels of intake, may be warranted. How much the intake of omega-3 fatty acids should be increased remains uncertain, although some conference participants felt that a dietary ratio of omega-6 to omega-3 fatty acids of about four-to-one might be desirable.

The balance between linoleic acid and α-linolenic acid in the diet, as well as the absolute amounts of these fatty acids, is important because both fatty acids are desaturated and elongated by the same enzyme system. Thus, α-linolenic acid is an important modulator of the metabolism of arachidonic acid. Emerging research has suggested a variety of benefits (e.g., decreasing elevated levels of blood triglycerides and reducing platelet aggregation) which might occur as a result of even a moderate intake of omega-3 fatty acids.

Conference proceedings will be published in book form by the Plenum Publishing Corp. of New York.