Pharmacological Research, Vol. 40, No. 3, 1999
Article No. phrs.1999.0495, available online at http://www.idealibrary.com on IDEAL®

HEALTH BENEFITS OF DOCOSAHEXAENOIC ACID (DHA)

LLOYD A. HORROCKS[a,b,*] and YOUNG K. YEO[c]

[a]Docosa Foods Ltd, 1275 Kinnear Road, Columbus, OH 43212-1155, USA, [b]Department of Medical Biochemistry, The Ohio State University, Columbus, OH, USA, and [c]Lipid Laboratory, Kyungpook National University, Taegu 635, Republic of Korea

Accepted 7 January 1999

Docosahexaenoic acid (DHA) is essential for the growth and functional development of the brain in infants. DHA is also required for maintenance of normal brain function in adults. The inclusion of plentiful DHA in the diet improves learning ability, whereas deficiencies of DHA are associated with deficits in learning. DHA is taken up by the brain in preference to other fatty acids. The turnover of DHA in the brain is very fast, more so than is generally realized. The visual acuity of healthy, full-term, formula-fed infants is increased when their formula includes DHA. During the last 50 years, many infants have been fed formula diets lacking DHA and other omega-3 fatty acids. DHA deficiencies are associated with foetal alcohol syndrome, attention deficit hyperactivity disorder, cystic fibrosis, phenylketonuria, unipolar depression, aggressive hostility, and adrenoleukodystrophy. Decreases in DHA in the brain are associated with cognitive decline during aging and with onset of sporadic Alzheimer disease. The leading cause of death in western nations is cardiovascular disease. Epidemiological studies have shown a strong correlation between fish consumption and reduction in sudden death from myocardial infarction. The reduction is approximately 50% with 200 mg day^{-1} of DHA from fish. DHA is the active component in fish. Not only does fish oil reduce triglycerides in the blood and decrease thrombosis, but it also prevents cardiac arrhythmias. The association of DHA deficiency with depression is the reason for the robust positive correlation between depression and myocardial infarction. Patients with cardiovascular disease or Type II diabetes are often advised to adopt a low-fat diet with a high proportion of carbohydrate. A study with women shows that this type of diet increases plasma triglycerides and the severity of Type II diabetes and coronary heart disease. DHA is present in fatty fish (salmon, tuna, mackerel) and mother's milk. DHA is present at low levels in meat and eggs, but is not usually present in infant formulas. EPA, another long-chain *n*-3 fatty acid, is also present in fatty fish. The shorter chain *n*-3 fatty acid, α-linolenic acid, is not converted very well to DHA in man. These longchain *n*-3 fatty acids (also known as omega-3 fatty acids) are now becoming available in some foods, especially infant formula and eggs in Europe and Japan. Fish oil decreases the proliferation of tumour cells, whereas arachidonic acid, a longchain *n*-6 fatty acid, increases their proliferation. These opposite effects are also seen with inflammation, particularly with rheumatoid arthritis, and with asthma. DHA has a positive effect on diseases such as hypertension, arthritis, atherosclerosis, depression, adult-onset diabetes mellitus, myocardial infarction, thrombosis, and some cancers.

KEY WORDS: docosahexaenoic acid, nervous system, cardiovascular disease, development.

* Corresponding author.

1043–6618/99/090211–15/$30.00/0

INTRODUCTION

Fat is an essential component of the diet [1]. On a fat-free diet, rats do not grow or reproduce. The essential fatty acids are the critical components of fat [2]. Essential fatty acids include linoleic acid and its omega-6 derivative, arachidonic acid. More recently, the vital role of alpha-linolenic acid and its omega-3 derivative, docosahexaenoic acid, has been recognised [3, 4]. The active components in both series are the longer chain acids such as arachidonic acid and DHA. These are produced by desaturation and elongation or obtained from the diet. A high ratio of linoleic acid to linolenic acid causes a depletion of the longer chain omega-3 fatty acids, including DHA, by competing for the enzymes necessary for desaturation and elongation.

Humans originally consumed a diet rich in the omega-3 fatty acids and low in saturated fatty acids because wild and free-range food animals have much higher contents of omega-3 fatty acids than do the present-day commercial livestock. The dietary supply of fatty acids previously contained a 1:1 ratio of omega-6 to omega-3 polyunsaturated fatty acids [5]. The present ratio in the US is greater than 10:1, causing a deficiency of the omega-3 fatty acids. The excess of omega-6 fatty acids stimulates the formation of arachidonic acid (ARA), the fatty acid precursor of prostaglandins and other eicosanoids that are involved in inflammation. Although some ARA is essential, the present high ratio may be responsible for the increased incidence of arthritis and other chronic inflammatory diseases. Much evidence supports the conclusion that an increased intake of linoleic acid and an elevated ratio of omega-6 to omega-3 fatty acids is a major risk factor for western-type cancers, thrombotic diseases, apoplexy, allergic hyperreactivity, and diseases for which anti-inflammatory drugs are effective [6]. Based on this evidence, the Japan Society for Lipid Nutrition recommends that the ratio of omega-6 to omega-3 fatty acids should be less than 4:1 for healthy adults and less than 2:1 for the prevention of the chronic diseases of the elderly. The World Health Organization [7] and others [8] are now recommending a ratio of between 3:1 and 4:1 for omega-6 to omega-3 fatty acids.

Whole ground flaxseed, a good source of α-linolenic acid (LNA), is now becoming popular in foods for cats and dogs [9]. The purpose is to reduce the n-6/n-3 ratios to the range of 4:1−10:1. This solves problems in pets such as dry skin, allergic reactions, and cancer. LNA must be elongated, desaturated, transported to and from peroxisomes, and then shortened from 24:6 to 22:6 in order to produce DHA [10]. Estimates for adult humans are that from 10 to 40 g of flaxseed oil are necessary for the production of 200 mg DHA per day [9]. This is at the lower end of the recommended daily intake of DHA.

NERVOUS SYSTEM: INFANTS

Adequate supplies of ARA and DHA are needed for brain growth and functional development of infants according to the members of the board of ISSFAL [11]. Both neural integrity and function can be permanently disturbed by deficits of omega-6 and omega-3 essential fatty acids during foetal and neonatal development [12, 13]. Breast-feeding provides ARA and DHA to infants. The levels of DHA in mother's milk vary considerably according to the diet of the mother. The levels of ARA and DHA are not affected by the levels in the diet of the precursors, linoleic acid and α-linolenic acid, so it is apparently necessary to supplement the mother's diet with preformed long-chain polyunsaturated fatty acids [14]. After the consumption of herring or menhaden oil by lactating women, the DHA levels in human milk are increased significantly within 6 h with maximum levels at 24 h [15].

DHA plays an important role in the maintenance of normal neural functions, a role that omega-6 fatty acids cannot fill. PC12 cells in culture were used as a model system. DHA and ARA had similar effects on the release and uptake of norepinephrine. The outgrowth of neurites induced by nerve growth factor was promoted by DHA and suppressed by ARA [16]. The suppression by ARA included inhibition of the synthesis of ethanolamine glycerophospholipids. Part of the unique function of DHA in the nervous system seems to relate to the synthesis of phospholipids for the membranes needed for neurite elongation.

During foetal development, DHA is preferentially transported across the placenta into the foetal circulation [17]. This probably involves specific proteins. The foetal brain can produce a limited amount of DHA from the precursor LNA. The foetal and infant liver may also produce some DHA [18], but probably not enough for optimal development.

Premature infants are born with deficits of DHA. A reduced supply of the precursors for membrane growth may contribute to the fragility of the periventricular vascular system and be responsible for the haemorrhage for which premature infants are at risk. The vascular network serving the developing brain must develop at a rapid rate to accommodate the brain growth occurring at that time. In addition, very low birth weight infants are unable to synthesise DHA and ARA in sufficient amounts from the linolenic acid and linoleic acid precursors [19]. Supplementation of their formulas with the amounts of DHA and ARA typical for human milk fat prevents the deficiencies [19].

Preterm infants were fed with mother's milk or

with formula containing only LA and LNA [20]. Those infants fed with mother's milk had an IQ that was 8.3 points higher at the age of 7.5–8 years. There was a dose–response relationship between the amount of mother's milk and IQ. Another group of preterm infants fed formula supplemented with DHA had a higher Bayley MDI (Mental Development Index) score at 12 months than controls fed the usual preterm formula [21]. This is evidence that DHA alone can improve performance on early tests of mental development. In a recent review, Crawford *et al.* [22] conclude that the present parenteral and enteral lipid nutrition for preterm babies is flawed and could be pathogenic. Preterm lipid nutrition should be based on normal placental lipid transfer to the foetus, not on fullterm milk composition.

Specific omega-3 fatty acid deficits may lead to deficits in learning ability because DHA is involved in cell signalling. DHA is the predominant structural fatty acid in the grey matter of the brain and retinal tissues in humans and other mammals. Humans obtain DHA primarily from their diets because they are capable of synthesising only small amounts of DHA. Infants acquire DHA and ARA, essential fatty acids in human tissues, initially *in utero* during pregnancy, and from their diet via their mother's milk. The content of DHA in the cerebral cortex is lower in formula-fed than in breast-fed infants [23]. DHA in the cerebral cortex is apparently dependent on the supply in the diet [24]. Adequate supplies of DHA and ARA in the diet may be particularly important for premature and low birth weight infants who may not get their full *in utero* allotment.

Many independent studies indicate that the mental development and visual acuity of infants are positively affected by breast feeding and that breast-fed infants have higher levels of DHA in their brain tissue and enhanced mental ability later in life when compared to those fed infant formula not containing DHA. Brain development in humans takes place primarily in the last trimester *in utero* and in the first 12 months of post-natal life and then at a slower pace up to 30 years of age.

Data on the healthful attributes of breast milk have prompted a trend among infant formula manufacturers to reformulate their products so that they more closely approximate breast milk. Infant formulas with DHA and ARA are now available in 40 countries [9]. The following are samples of published data indicating that DHA in the diet may be associated with mental and visual development of infants.

Large-scale retrospective studies, involving between 700 and 13,000 persons, have evaluated development of intelligence in infants, children and adolescents as a function of breast feeding *vs* formula feeding during infancy. These studies have demonstrated that pre-term infants fed human milk during infancy exhibited a 5–12 point higher intelligence quotient (IQ) later in life than similar groups of babies fed conventional formulas [25]. This difference was also apparent for term infants, although it was not as large (2–5 points). In addition, the measured IQ in the term infants was positively correlated with the duration of breast-feeding.

DHA and ARA levels in erythrocyte phosphatidylcholine correlate positively with the developmental quotient of children at age 2 [26]. These 20 children had early diets of human milk, standard formula, or formula enriched with long-chain polyunsaturated fatty acids. These further support the conclusion that DHA is the substance in breast milk that is responsible for the difference in IQ described in the paragraph above.

Several studies [27–29], using data from term and pre-term infants that died early in infancy, have indicated that breast-fed babies had higher levels of DHA in the brain than formula-fed babies. This was true for both cerebral cortex and erythrocytes for 35 term infants [24, 25, 28]. The DHA in the cerebral cortex increased with age, primarily due to the length of breast-feeding. Long-term benefits of dietary DHA to the term infant have not yet been proved rigorously, although infants with higher levels of DHA have faster development of electrophysiological and behavioral functions. Rhesus monkeys with a severe deficiency of DHA were placed on a diet enriched in fish oil [30]. The DHA content of the ethanolamine glycerophospholipids increased from 3.9 to 28.4% over a 12-week period. The DHA content of the erythrocyte phospholipids reflected the DHA content of the cerebral cortex. This shows that the DHA status of human cerebral cortex can be monitored by analysis of erythrocytes.

The disparity in neural maturation between breast-fed and formula-fed term infants was studied with three groups of normal term infants. If mothers had chosen to bottle feed, infants were randomised to regular formula or a formula supplemented with fish oil. The third group was breast-fed. Red cell fatty acids and growth were measured at day 5 and at 6, 16, and 30 weeks of age. The visual evoked potential (VEP) acuity was measured at the two older ages. VEP acuities were worse for those on regular formula at both 16 and 30 weeks of age. The level of DHA in the red cells consistently correlated with VEP acuity. No differences were seen in growth. As assessed by VEP acuity, DHA appears to be an essential nutrient for the optimum neural maturation of term infants [31].

Foetal alcohol syndrome is a severe irreversible impairment of neurological development and function caused by chronic alcohol consumption during pregnancy. Moderate ethanol intake is associated with reduced intelligence in children at 4 years [32]. A high intake of ethanol during pregnancy results in infants with severely impaired intelligence, hyperactivity, low attention span, and abnormal motor function [33–36]. A guinea pig model of foetal alcohol

syndrome leads to decreased DHA in brain phospholipids, together with impaired motor function. Supplementation of guinea pigs with 130 mg day^{-1} of DHA in tuna oil completely prevented the ethanol effect on the DHA content in the brain phospholipids [37].

Formula-fed babies, compared to breast-fed babies, have twice as many neurological abnormalities at 9 years of age. A Dutch study assessed the neurological status of 526 children and concluded that the frequency of neurological abnormalities at 9 years of age was twice as high in formula-fed babies as compared to breast-fed babies. The characteristics of DHA deficiency in rhesus monkeys include reduced learning ability, abnormal electroretinogram, impaired vision, and polydipsia (excessive thirst) [4].

Premature infants are also at greater risk for learning disabilities (dyslexia, attention deficit disorder, etc.) and behavioural problems. A mixture of evening primrose oil and a fish oil, Efalex™ from Scotia Pharmaceuticals, benefits many dyslexic children [38]. The concentrations of ARA, EPA, and DHA in plasma phospholipids were significantly lower in 53 subjects with attention-deficit hyperactivity disorder (ADHD) than in 43 control subjects. Many children with ADHD have altered fatty acid metabolism [39]. This group at Purdue University is planning nutritional experiments with similar subjects with the objective of raising the levels of ARA and DHA in the plasma.

Peroxisomal disorders, such as adrenoleukodystrophy, have defects in the peroxisomes that cause impaired synthesis of ether glycerophospholipids. These include the ethanolamine plasmalogens that are important components of myelin. Myelination is severely impaired in these children. Daily oral doses of 100–600 mg of DHA ethyl ester were given to five patients [40]. Blood levels of DHA rose to normal levels within a few weeks. In the three youngest patients, the myelination became nearly normal and clear improvement was seen in the other two. DHA synthesis is prevented by the peroxisomal defect and must be bypassed with dietary DHA in these infants. DHA seems to be necessary for plasmalogen synthesis.

Young cystic fibrosis patients are also deficient in DHA and other essential fatty acids [41]. An imbalance between ARA and DHA in the cell linings of the pancreas, lungs, and gastrointestinal tract was proposed to explain the symptoms of cystic fibrosis [42]. CFTR (−/−) mice, who mimic symptoms of the disease, were fed a triglyceride oil from Martek that is high in DHA. The cystic fibrosis symptoms in the mice were reversed and they approached the level in the control mice.

Phenylketonuric and other patients with inborn errors of metabolism are placed on protein-restricted diets. The levels of DHA in the plasma phospholipids of these patients are less than one-third of the level in controls [43]. DHA supplementation is recommended for these patients because they are usually deficient in psychomotor development. This suggests that long-chain PUFA are semi-essential for children far beyond the breast-feeding period.

A 'suppression system' through the limbic system may be involved in the 'Teacher's Signal' to depress neural activity that would otherwise contribute to error responses. This suppression of neural activity is lacking in behavioural hyperactivity. The limbic system circuit is from basal ganglia through the thalamus to the cerebral cortex. One hypothesis is that behavioral hyperactivity in laboratory animals and in humans is linked to the deficiency of *n*-3 fatty acids in the brain [44]. This lack of suppression of neural activity interferes with error correction during learning. This would explain the observations on learning performance in rats fed safflower oil (LNA-deficient) compared with rats fed perilla oil (LNA-enriched). The groups were similar in the number of correct responses, but the safflower oil group had markedly more incorrect responses, particularly with reversal of the correct stimulus from bright light to dim light, in a brightness-discrimination task [45, 46]. The rats fed safflower oil had a brain DHA content approximately half of the normal level. In the safflower group, the brain DHA was partially replaced with 22:5 *n*-6. In addition, the rats fed safflower oil had a significantly decreased density of synaptic vesicles in the hippocampus CA1 region after, but not before, the learning task [47, 48]. Thus, there was an associated effect of the learning task and the *n*-3 fatty acid deficiency [44]. This indicates that during the use of the synapse, fatty acid turnover in the membrane phospholipids resulted in changes in composition dependent on the fatty acids available for replacement, with resulting changes in the strength of the synapse. Morphological changes in synapses in the hippocampus caused by adequate *n*-3 fatty acids are related to learning performance [47].

In adults, part of the DHA is made in the liver by elongation and desaturation of LNA. The extent of this synthesis in human infants was assessed by determination of the fatty acid compositions of brain and liver tissues from infants who died within the first 6 months of life from sudden infant death syndrome. The infants were breast-fed or formula-fed. The latter had received a regular formula containing less than 0.4% LNA or a different formula containing 1.5% LNA. The content of DHA was lower in cerebral cortex phosphatidylethanolamine and phosphatidylserine in both formula-fed groups. This was compensated by a higher content of DPA, docosapentaenoic acid, in term infants and with 20:3 ω9, Mead acid, and 22:3 ω9 in one preterm infant [29]. The contents of ARA and DHA in the liver

were lower in both formula-fed groups. The DHA content in formula groups was lowest at 3 months of age. Very little conversion of LNA to DHA occurs in the first few months of fife. Thus, preformed DHA and possibly ARA should be included in the diet for at least the first 16 weeks of life [49]. However, a study comparing infants fed formula with at least 0.7% α-linolenic acid with breast-fed infants showed no significant differences in preferential looking acuity or recognition memory in healthy full-term, infants at 9 months of age [50].

Also in the mouse, DHA reaches the brain and retina more efficiently if fed as DHA instead of the precursor, LNA [51]. Rats were fed an omega-3-deficient diet up to 5 weeks of age [52]. For the next 3 weeks, their diet was supplemented with rapeseed oil as a source of LNA or with fish oil as a source of EPA and DHA. Approximately twofold more vegetable oil than fish oil was needed to reach the same level of DHA in the tissues. The recovery of DHA in nervous tissues was more rapid with fish oil than with vegetable oil [52].

NERVOUS SYSTEM: ADULTS

Granule neurons in the dentate gyrus of the hippocampus continue to proliferate throughout the life of adult monkeys [53]. The numbers of these proliferating cells are reduced significantly by stress. This recent observation contradicts the previous idea that brain cells do not divide after early development. The formation of new cells in the hippocampus helps explain why dietary DHA is important for the maintenance of the brain and of learning during aging.

A genetic strain of rats with spontaneous hypertension has been produced. Dietary DHA suppresses the development of hypertension and stroke-related behavioral changes, thus prolonging the life span of these spontaneously hypertensive rats [54]. The DHA in the diet was correlated with decreased systolic blood pressure, restoration of learning performance in a passive avoidance response test, and with hippocampal acetylcholine levels. Dietary DHA apparently ameliorates the learning performance failure caused by cholinergic dysfunction [54].

Long-chain polyunsaturated fatty acids, particularly DHA, may reduce the development of unipolar depression [55]. The occurrence of depression correlates well with the deficiency of essential omega-3 fatty acids [56, 57]. For example, depressed patients were instructed to increase fish consumption in a 5-year study [58]. Measures of depression and aggressive hostility were reduced significantly. The rate of depression is lower in societies consuming large amounts of fish. For example, in Japan the rate is 0.12%, whereas in the US the rate is 3.0%. The fish consumption rates are 67 and 22 kg per person per year, respectively. Similar findings were reported for Taiwan and Korea. A correlation of fish consumption in different countries with the prevalence of major depression gave a highly significant decrease of depression with increasing fish consumption [59]. An extreme case is New Zealand with less than 18 kg per person per year fish consumption and 5.8% persons with major depression.

Violent impulsive offenders in Finland have a much higher ratio of omega-6 to omega-3 PUFA in their serum, when compared with diet-matched control subjects [60]. In the review by Drs Hibbeln and Salem from the National Institute of Alcohol Abuse and Alcoholism [55], they state, 'Just as increased consumption of saturated fat and the altered ratio of *n*-6 to *n*-3 intake is believed to have increased the incidence of atherosclerosis in the last century [61], it is suggested here that decreasing *n*-3 essential fatty acid intake may also affect the nervous system, in early development or adulthood, to increase vulnerability to depression'.

Chronic alcohol intoxication depletes DHA from membranes of the neurons, leading to the common secondary depression in alcoholism. The increased lipid peroxidation associated with alcohol may cause a decrease in DHA in the brain. Thus, depression may resolve during sobriety as PUFA reaccumulate [55]. DHA deficiency may also be associated with susceptibility to multiple sclerosis and the high incidence of depression in patients with multiple sclerosis. Geographical patterns of omega-3 fatty acid intake correlate inversely very well with the incidence of both multiple sclerosis and depression [55]. Maternal depletion of DHA for the developing foetal nervous system is one factor in post-partum depression [55]. Low levels of DHA are also associated with senile dementia (Alzheimer disease) and schizophrenia.

DHA is also important for the brain during aging. A study was done with a group of men aged 69–89 years [62]. Cognitive impairment was evaluated with a 30-point Mini-Mental State Examination given in 1990 and 1993. Food intakes were estimated in 1985 and 1990. After adjustments for all other known variables, high LA intake was associated with cognitive impairment and high omega-3 PUFA intake through fish consumption was inversely associated with cognitive impairment and with cognitive decline between 1990 and 1993. Thus a high ratio of omega-6 to omega-3 fatty acids in the diet was bad and fish in the diet was good for maintenance of the cognitive functions of the brain.

The prevalence of Alzheimer disease correlates positively with high fat and high total calorie consumption and negatively with fish consumption [63]. Fish oils decrease inflammation and ischaemia. High fat and high calorie diets are associated with a high

n-6/*n*-3 ratio and inflammatory responses. Antioxidants, fish oil, and non-steroidal anti-inflammatory drugs are all associated with delaying the onset of sporadic Alzheimer disease [64, 65].

A 4:1 ratio of omega-6 to omega-3 fatty acids may be optimal. This ratio of LA to LNA, known as SR-3, has given the best results in learning tasks with rats [66]. A 4-week study with 2 ml day^{-1} of this supplement was carried out with 100 Alzheimer patients, 60 receiving this preparation and 40 receiving the placebo. During this short time, improvements in mood, cooperation, appetite, sleep, ability to navigate in the home, and short-term memory were found in treated patients. Overall improvement was reported for 49 of the 60 patients and no improvement for 11 patients. In the placebo group, 30 were unchanged, five were worse, and five were improved [67]. Supplementation with essential fatty acids in the proper ratio of omega-6 to omega-3 fatty acids can be helpful for demented persons.

Humans can be deficient in omega-3 essential fatty acids [68]. Rhesus monkeys with diets deficient in these fatty acids have low levels of DHA in the cerebral cortex and retina. The reversibility of such deficiencies in juvenile monkeys began as early as 1 week after fish oil feeding and was complete at 12 weeks. Monkey, and presumably human, cerebral cortex has a remarkable capacity to change its fatty acid composition. The turnover rate of these fatty acids is much greater than generally believed [30]. The development of the visual system of human infants is dependent in part on the availability of DHA. The effect is most apparent in preterm infants, suggesting that an exogenous source of DHA may be needed during the time of rapid development of the retina [69]. As measured in red blood cells and plasma of the mothers, mothers of preterm infants have higher *n*-6/*n*-3 ratios than do mothers of normal term infants. Thus, maternal DHA deficiency is associated with an increased risk of preterm birth [70] and both arachidonic acid and DHA are essential for harmonious foetal development [71].

In rats, a chronic administration of 200 mg kg^{-1} day^{-1} of DHA for 21 days did not affect the level of DHA in the hippocampus, but did show some increase in the frontal cerebral cortex. The rats were subjected to an experimental stroke by four-vessel occlusion and tested in a spatial learning task. The spatial learning deficit and the loss of neurons in the CA1 region of the hippocampus was less in the rats given DHA than in control rats. DHA may be protective for hippocampal neurons involved in spatial learning [72].

A mechanism for neuronal protection in the CNS by DHA may be the inhibition of apoptosis induced by sphingosine. The cytoplasmic phospholipase A_2 specific for glycerophospholipids containing arachidonate is inhibited by DHA [73]. Arachidonate metabolites participate in the process of apoptosis in response to tumour necrosis factor [74]. With HL60 cells in culture, DHA in the medium inhibits apoptosis induced by sphingosine but not that induced by *N*-acetyl sphingosine [75]. EPA and other unsaturated fatty acids did not show this effect.

Cytoplasmic phospholipase A_2 is probably involved because an inhibitor of that enzyme was also effective and DHA was only effective after it was incorporated into the glycerophospholipids.

CARDIOVASCULAR DISEASE

The leading cause of death in western nations is cardiovascular disease [76]. The increase in deaths due to coronary heart disease in these nations has been blamed on the increased consumption of saturated fats. The American Heart Association estimates that 57 million Americans have cardiovascular disease, causing 954,000 deaths annually and costing $259 billion per year. Hypolipidemic pharmaceutical agents, such as cholestyramine, colestipol, lovastatin, pravastatin, other statins, clolibrate, and niacin are effective in various degrees in reducing serum triglycerides and LDL-cholesterol and increasing HDL-cholesterol. However, these drugs also have significant side effects. Cholestyramine and colestipol disturb the GI tract. The statins may elevate liver enzymes, disturb the GI tract, and cause dysfunctions of the CNS. Patients with hepatic or renal disorders cannot use clofibrate. Niacin is associated with vasodilation with flushing episodes and other side effects. Many billions of dollars are spent annually on these drugs. Better nutrition with more long-chain omega-3 fatty acids, especially DHA, can produce the same lipid changes and positive effects with no side effects and much less expense.

Low-fat diets are often recommended for the reduction of cholesterol and prevention of coronary artery disease. The effects of a diet with 55% of energy from carbohydrate and 30% from fat were compared with a diet with 40% from carbohydrate and 45% from fat [77]. The subjects were 42 persons with Type II diabetes treated with glipizide. After 14 weeks, the subjects on the low-fat diet had 24% higher plasma triglycerides, daylong glucose up 12%, and insulin up 9%. The conclusion was that the high-carbohydrate, low-fat diet caused persistent deterioration of glycemic control. The effects of Type II diabetes were made worse by the diet with only 30% of energy from fat. Of course, the quality of fat is very important, particularly the ratio of *n*-6 to *n*-3 polyunsaturated fatty acids.

DHA supplements increase the HDL/LDL cholesterol ratio and decrease the total cholesterol/HDL ratio, suggesting a decreased risk for coronary artery disease. The association of DHA deficiency with depression is the reason for the robust positive

correlation between depression and coronary artery disease and myocardial infarction. Premorbid depression predicts coronary artery disease and poor survival outcome. Chronic stress mobilises polyunsaturated fatty acids from neuronal membranes and increases peroxidation of the fatty acids. This increases the vulnerability to depression and to coronary artery disease.

At least half of the deaths from coronary artery disease are sudden cardiac deaths with fatal arrhythmia due to ventricular fibrillation. Epidemiological studies have shown decreased cardiovascular disease with greater fish oil consumption. Fish oil not only reduces triglycerides in the blood and decreases thrombosis, but also prevents cardiac arrhythmias. A monthly intake of 5500 mg of omega-3 fatty acids from fish was associated with a 50% reduction in the risk of primary cardiac arrest [78]. In a 30-year study of middle-age men, there was an inverse association between fish consumption and death from coronary heart disease, particularly for non-sudden death in this study [79].

The DART study was a 2-year intervention study with 2033 men recovering from myocardial infarction [80]. Those men advised to eat fish or take fish oil supplements had a cardiac death rate of 78 per 1000, whereas the rate for those without fish advice was 116 per 1000. The latter included those advised to increase polyunsaturated fatty acids while reducing total fat and those advised to increase cereal fibre intake. The conclusion was that two or three portions of fish per week may reduce mortality in men who have recovered from myocardial infraction.

Deaths from acute myocardial infarctions are mostly due to ventricular arrhythmias, primarily ventricular fibrillation. The intravenous infusion of omega-3 fatty acids from fish oils prevents ischaemia-induced ventricular fibrillation in dogs and rats. An emulsion of free long-chain omega-3 PUFA prevented ventricular fibrillation in ten of 13 dogs tested [81]. The long-chain omega-3 PUFA slowed the heart rate, shortened the electrical action potential duration, reduced left ventricular systolic pressure, and prolonged the electrocardiographic atrial–ventricular conduction time [81]. The electrophysiologic effects of these free acids are associated with blockade of the fast voltage-dependent sodium channels [82] by binding of the fatty acid to the channel protein thus prolonging the inactivated state [83]. A possible mechanism for the prevention of arrhythmias by omega-3 fatty acids from fish is the blockage of fast voltage-dependent sodium channels. Other possible mechanisms include effects on calcium channels and on cell signalling mediated through polyphosphoinositides [76].

The dietary intake of omega-3 fatty acids from seafood has been associated with a reduced risk of primary cardiac arrest (heart attack). A population-based case control study was done with 827 cases and controls. Subjects with heart attack had a dietary intake of 4.3 ± 6.0 (SD) g of EPA and DHA per month, whereas control subjects had a dietary intake of 5.3 ± 5.6 (SD) g of EPA and DHA per month ($P = 0.02$). An inverse relation was found for dietary intake of EPA and DHA and the risk of primary cardiac arrest. Compared with no dietary intake of EPA and DHA, an intake of 5.5 g (approx. 0.2 oz) of omega-3 fatty acids per month (the equivalent of one fatty fish meal per week) was associated with a 50% reduction in the risk after adjustment for confounding factors such as age, smoking, family history, physical activity, and education. Even an intake of only 2.9 g of EPA and DHA per month, the equivalent of two fatty fish meals, was associated with a 30% reduction in risk. The conclusion of these researchers from the Universities of Washington, Michigan and Minnesota is that dietary intake of omega-3 polyunsaturated fatty acids from seafood is associated with a reduced risk of primary cardiac arrest [78].

A prospective study followed up on these findings [84]. More than 20,000 US male physicians were followed for 11 years. There were 133 sudden deaths. After controlling for appropriate factors, the consumption of at least one fish meal per week was associated with a risk reduction of 52% for sudden death ($P = 0.03$) and with a reduced risk of total mortality.

Another prospective study involved more than 80,000 female nurses with 14 years of follow-up with 939 cases of non-fatal myocardial infarction or death from coronary heart disease [85]. Multivariate statistical analyses included percentages of energy from specific types of fat. Comparing with energy from carbohydrates, 5% of energy intake from saturated fat increased the risk of coronary heart disease by 17%. For 2% of energy intake from *trans* fatty acids, the increased risk was 93%. The risk was reduced by 19% by monounsaturated fat and 38% by polyunsaturated fat at 5% of energy intake in comparison with energy from carbohydrates. The conclusion is that replacement of saturated and *trans* unsaturated fats with non-hydrogenated monounsaturated and polyunsaturated fats is more effective in preventing coronary heart disease in women than reducing overall fat intake.

Trans unsaturated fatty acids are present in hydrogenated fats such as margarines and shortenings. These fatty acids inhibit the desaturation of LA and LNA to long-chain polyunsaturated fatty acids. In man, this is manifested by lower levels of HDL and higher levels of LDL. The presence of *trans* unsaturated fatty acids in the diet is the cause of 30,000 premature deaths per year [86].

EPA and DHA are both present in fish oils. Fish oils generally contain more EPA than DHA and EPA is known to be a substrate for cyclooxygenase. Thus, EPA was presumed to be the active compo-

nent of fish oils for cardiovascular protection. Purified ethyl esters of these two fatty acids were tested for their ability to suppress arrhythmias induced by ischaemia, to retard development of hypertension in rats genetically predisposed to hypertension, to offset the constriction caused by thromboxane is isolated blood vessels, and to reduce the excretion of protein in the urine in a model of kidney failure caused by hypertension. DHA was more effective than EPA in all of these tests. The results imply that DHA is the principal active component in fish oil for cardiovascular protection [87]. Cultured rat cardiomyocytes have increased contraction velocity and arrhythmias through stimulation of α_1-adrenoceptors. Pretreatment for 3 days with DHA decreased the stimulated α_1-adrenoceptor formation of inositol trisphosphate, a calcium-mobilising second messenger. Thus, inhibition of the phosphoinositide pathway by chronic DHA may contribute to the effects of fish oil in preventing fatal arrhythmias in myocardial ischaemia [88].

Coronary bypass surgery is often complicated by the occlusion of the grafted veins. A randomised controlled study showed a significantly lower rate of occlusion in the group consuming 4 g fish oil per day as compared with the control group [89].

A long-term study in Copenhagen, Denmark has examined the risks of ischaemic heart disease as a function of serum lipid parameters. The combination of high triglyceride and low HDL-cholesterol was at least as powerful a predictor of ischaemic heart disease as high LDL-cholesterol. The former is characteristic of insulin-resistant subjects. They concluded that efforts to prevent ischaemic heart disease should include intervention against high triglycerides and not just against hypercholesterolemia [90].

Icelanders consume a large amount of fish and have a relatively low mortality from coronary heart disease. A rural population from Iceland was compared with residents of Manitoba of Icelandic descent [91]. The Icelandic-Canadians had lower levels of plasma LDL-cholesterol. and HDL-cholesterol, but higher levels of plasma triglycerides. Their plasma phospholipids were higher in saturated, monounsaturated, and omega-6 polyunsaturated fatty acids, but threefold lower in omega-3 polyunsaturated fatty acids. These two groups are genetically similar. Thus, the differences in mortality correlate with the ratio of omega-6 to omega-3 fatty acids in the diet and the plasma triglyceride levels. Cholesterol levels are the opposite to that expected for a coronary disease risk factor.

The Western Electric Study in Chicago included 2107 men aged 40–55 years. After 30 years of follow-up, the stroke rates are highest for the subgroup consuming the most fish, but the results do not support the hypothesis that fish consumption is inversely associated with strokes [92]. Dietary histories were used to divide the men into four groups with no, low, moderate, and high levels of fish consumption. There have been 430 deaths from coronary heart disease, including 293 deaths from myocardial infarction. Deaths from any cause included 1042 of the 1822 men used in the follow-up. Men in the group with highest fish consumption compared with those with no fish consumption had a much lower risk of death from coronary heart disease and myocardial infarction, and a somewhat lower risk, but statistically not significant, of death from all causes. All of the lower risk for coronary heart disease and all causes was attributable to differences in death from myocardial infarction. For the high fish consumption group, the relative risk of death from myocardial infarction was 0.56 compared with 1.00 for the no fish consumption group. These results show an inverse association between fish consumption and death from coronary heart disease ($P = 0.007$) [79].

In the pathogenesis of atherosclerosis, vascular smooth muscle cell growth is an important component [93]. These cells have the potential to proliferate and to accumulate lipids. Cyclins and cyclin-dependent kinases control progression through the eukaryotic cell cycle and thus the proliferation of cells. DHA and EPA inhibit DNA synthesis through G_1 cyclins, cyclin-dependent kinases, and cyclin-dependent kinase inhibitors (p27) and stop the progression from G_1 to S phase [93]. Oleic and linoleic acids had no effect. The same mechanism may also be operative in tumour cells whose proliferation is inhibited by DHA and EPA. EPA and DHA inhibit the proliferation of vascular smooth muscle cells. This could explain part of the anti-atherosclerotic effect of fish oils [94]. In smooth muscle cells from foetal rat aorta, EPA, DHA and DPA activate a K^+ current and also inhibit receptor-mediated non-selective cation currents. Thus, these *n*-3 fatty acids may be important for the regulation of vascular tone [95]. The sustained outward current through certain neuronal voltage-gated K^+ channels is inhibited by free DHA by interaction with an external domain on the channel. Zn^{2+} antagonizes the inhibition [96].

Platelet function and blood coagulation play important roles in coronary artery disease. Several studies with fish diets or fish oil supplements have demonstrated decreased platelet aggregation, thromboxane production, and prolonged bleeding time. The effects of α-linolenic acid from flaxseed oil were compared with EPA plus DHA from fish oil in healthy human subjects. The fish oil decreased serum total cholesterol and triacylglycerols, but flaxseed oil had no effect. Both oils decreased collagen-induced platelet aggregation and thromboxane production [97]. Thus, the 18-carbon omega-3 fatty acid was as effective as fish oil for haemostatic factors, but only the fish oil reduced serum lipid cardiovascular risk factors. In a rat model of arterial

thrombus formation, the optimal reducing effect of long-chain omega-3 fatty acids was at 4% of the diet [98]. Comparisons of EPA and DHA gave similar results on thrombosis tendency, platelet aggregation, and thromboxane B_2 formation. These two fatty acids seem to be equivalent in affecting thrombosis.

The effects of fish oil and flaxseed oil, 35 mg kg^{-1} day^{-1} for 3 months, were compared in 26 subjects. A typical western diet with a low ratio of polyunsaturated fatty acids to saturated fatty acids was consumed by 15 of the subjects. For the latter subjects, fish oil reduced the plasma triacylglycerol levels between 24 and 27%. In both groups of subjects, neither fish oil or flaxseed oil affected the concentrations of LDL or HDL cholesterol. This intake of fish oil may have some protective value in healthy individuals by reducing atherogenic risk factors, especially in those persons consuming the typical western diet [99].

In some patients with elevated serum triacylglycerol levels, supplements containing EPA and DHA have increased serum levels of LDL cholesterol. A group of 26 subjects with combined hyperlipidaemia, LDL cholesterol greater than 130 mg dl^{-1} and triacylglycerols greater than 150 mg dl^{-1}, received DHA at dosages of 1.25 or 2.5 g day^{-1} for 6 weeks. Reductions of serum triacylglycerols were 20.9 and 17.6%, respectively, with no change in a placebo group. Small increases in HDL cholesterol with no change in LDL cholesterol were seen in all groups. A low fat, high carbohydrate diet is often recommended for patients with combined hyperlipidaemia. This diet usually exacerbates the lipid abnormalities, whereas supplementation of the diet with DHA may be useful clinically [100].

The EPA and DHA in fish oil accumulate in different compartments in the body. With cultured human endothelial cells, DHA selectively attenuates expression of proatherogenic and proinflammatory proteins, possibly explaining a positive effect of DHA on atherosclerosis [101], whereas EPA is apparently the more potent inhibitor of platelet aggregation [102, 103]. A double-blind, placebo-controlled, parallel design intervention study was done with 234 healthy non-smoking men for 7 weeks [104]. These men received 3.8 g EPA per day, 3.6 g DHA per day, or 4.0 g corn oil per day. When compared with the corn oil group, serum triacylglycerol levels were 26% lower with DHA and 21% lower with EPA. HDL cholesterol increased in the DHA group, but not in the EPA group [104]. Postprandial triglyceridemia was suppressed by 19 and 49% after prolonged ingestion of EPA and DHA, respectively [105]. DHA is more effective than EPA in reducing postprandial triglyceridemia. The serum phospholipids showed some conversion of DHA to EPA in the DHA group, and some conversion of EPA to DPA, but no conversion of EPA to DHA in the EPA group [105].

Table I
Fatty acid composition (%) of high-oleic acid oils

Fatty acid	*Sunflower*	*Sunflower*	*Olive*	*Olive*	*Canola*	*Canola*
16:0	5	6	14	12	7	6
18:1	75	82	66	74	54	60
18:2 *n*-6	15	9	17	11	28	22
18:3 *n*-3	< 0.2	< 0.2	0.5	0.6	7	8

This suggests that DHA is essential in the diet for those functions specific for DHA.

EPA and DHA are partially interconvertible. DHA is formed from EPA by elongation and desaturation. If only DHA is included in the diet, part of the DHA is retroconverted to EPA by partial β-oxidation. A daily supplement of 1.62 g DHA over a period of 6 weeks increased serum phospholipid DHA from 2 to 7 mol% in both vegetarians and omnivores; EPA also increased. Based on the serum phospholipid results, these subjects retroconverted approximately 9.4% of the DHA to EPA [106].

Olive oil in the Mediterranean-type diet seems to have beneficial effects on coronary heart disease. It is not known if this is due to the high level of oleic acid or to minor components, such as flavonoids and phenolics, in the olive oil [107]. Rats were fed diets containing olive oil, high-oleic sunflower oil, or a canola-type rapeseed oil [108]. The canola oil had a higher proportion of linoleic acid and a much higher proportion of LNA than the other two oils (Table I). Thus, only the canola oil had a ratio of *n*-6/*n*-3 of less than 4.

The results of fatty acid analysis of the choline glycerophospholipids were similar to those for the ethanolamine glycerophospholipids, but with lower proportions of polyunsaturated fatty acids (PUFA). The PUFA in the heart and liver of the sunflower group were quite different from those in the olive and canola groups (Table II). The *n*-6 docosapentaenoic acid (DPA) was much higher in the sunflower and olive groups than in the canola group. This might be due to sufficient LNA in the canola group diet to prevent *n*-3 PUFA deficiency. High levels of DPA are a sign of PUFA imbalance with a lack of *n*-3 PUFA. Surprisingly, the olive group contained DHA at levels nearly equal to those in the

Table II
Polyunsaturated fatty acids (%) in the ethanolamine glycerophospholipids in liver and heart

Fatty acid	*Heart sunflower*	*Heart olive*	*Heart canola*	*Liver sunflower*	*Liver olive*	*Liver canola*
20:4 *n*-6	24.9	24.5	19.9	29.1	32.5	30.2
22:4 *n*-6	2.7	3.1	1.3	1.4	1.1	0.1
22:5 *n*-6	11.7	9.7	0.2	4.4	2.5	tr
22:5 *n*-3	0.5	1.8	6.1	0.3	1.2	2.5
22:6 *n*-3	7.4	23.0	31.7	3.9	14.8	17.1
n-3/*n*-6	0.2	0.6	1.5	0.1	0.4	0.5

canola group and much higher than those in the sunflower group. Thus, the high level of oleic acid is not responsible for the DHA content, because the sunflower group ingested the highest level of oleic acid. Low levels of LNA are present in the olive oil. This LNA must have been channelled into DHA synthesis, perhaps by inhibition of the δ-6 desaturase decreasing the conversion of linoleic acid to ARA [108]. These results are consistent with those of others [109, 110]. The heart and vasculature are protected against atherosclerotic changes by the inclusion of DHA in the membrane structure. Olive oil and especially canola oil promote the inclusion of DHA and exclusion of *n*-6 DPA. These effects may be the reason for the low prevalence of coronary heart disease in persons consuming a Mediterranean-type diet.

CANCER

The proliferation of several types of tumour cells is stimulated by arachidonic acid, an *n*-6 fatty acid that is a precursor of prostaglandins and lipoxygenase products. Human prostate cancer cells were grown *in vitro*. Inhibitors of 5-lipoxygenase inhibited the growth stimulatory effect of arachidonic acid. Addition of the product of 5-lipoxygenase, 5-HETE, stimulated the proliferation similarly to arachidonic acid and overcame the effects of the inhibitors [111]. When human breast cancer cells are grown in athymic nude mice, diets rich in linoleic acid with corn oil stimulate growth and metastasis, whereas diets with fish oil exert suppressive effects. This was confirmed with diets containing linoleic acid, EPA or DHA at 8% of the diet. The occurrence and severity of lung metastases were reduced in groups fed EPA or DHA. The effects of fish oil are due to the EPA and DHA in the fish oil and the mechanism likely involves inhibition of eicosanoid synthesis from ARA [112]. Apoptosis is a normal mechanism for the removal of tumour cells. ARA suppresses apoptosis of W256 carcinosarcoma cells in culture. In this study, 12-HETE and 15-HETE, but not 5-HETE, also prevented apoptosis [113]. Other fatty acids displaying some suppression of apoptosis included LA, LNA, and elaidic acid, the trans form of oleic acid. No suppression was observed with oleic acid or with DHA.

Milk fat contains numerous anticarcinogenic components including conjugated linoleic acid, sphingomyelin, butyric acid and ether lipids. Conjugated linoleic acid inhibits the proliferation of human malignant melanoma, colorectal, breast and lung cancer cells *in vitro*. Animal studies have shown inhibition of mammary tumorigenesis. Animal studies have compared the incidence of tumours after feeding milk fat or butter with feeding linoleic acid-rich vegetable oils or margarines. Diets with dairy products are associated with less tumour development than with linoleic acid-rich vegetable oils or margarines [114].

A recent review has emphasized the consistency of information regarding the effects of various types of fatty acids [115]. Results on cancer protection by oleic acid are not convincing because the effect could be due to a lower intake of linoleic acid. Conjugated linoleic acid, found in milk fat, produces significant cancer protection in concentrations less than 1%. This effect is apparently independent of other fatty acids. A suppressive effect of long-chain omega-3 PUFA is observed whenever the effect is not overwhelmed by linoleic acid, an omega-6 acid.

Weanling rats were fed with diets containing corn oil, safflower oil, or the DHA oil from Martek. The diets with a high *n*-6/*n*-3 ratio, corn oil or safflower oil, were both hypercholesterolemic. The corn oil at 5% by weight was also hypertriglyceridemic. The group fed DHA oil had similar cholesterol levels and lower triglyceride levels than the group fed standard chow. The DHA oil group also had a twofold higher cellularity of bone marrow. The latter observation suggests that DHA supplementation may be useful in adjuvant chemotherapy [116].

INFLAMMATION

The most widespread inflammatory disease is rheumatoid arthritis affecting more than 2,500,000 Americans with 200,000 new cases each year. Current therapy includes non-steroidal anti-inflammatory drugs such as aspirin and glucocorticoids and more potent drugs such as gold compounds, penicillamine and methotrexate. All of these drugs have considerable side effects. Increased levels of DHA and EPA in the diet of persons with rheumatoid arthritis should alleviate the pain and inflammation in their joints.

The effects of dietary fatty acids on inflammation were studied with carrageenan-induced swelling of footpads in rats. After 15 days of the diets, the swelling was reduced in the EPA and DHA groups, compared with the control groups. Swelling was correlated with the proportion of ARA in the polyunsaturated fatty acids [117].

EPA and DHA possess anti-inflammatory properties and may alter lymphocyte, monocyte, and macrophage functions. Three groups of guinea pigs were tested for resistance to infection by *Mycobacterium tuberculosis*. This depends on the combined action of T lymphocytes and macrophages. The group fed a relatively large amount of EPA and DHA had more mycobacteria in the spleen and a greater progression of disease than groups fed a small or large amount of LA [118]. Too much long-chain omega-3

fatty acid in the diet can affect the resistance to this bacterium in guinea pigs.

ASTHMA

Asthma is a chronic lung condition characterized by three airway problems, obstruction, inflammation, and hyperresponsiveness. Allergic asthma is triggered by an allergen, such as pollen. Non-allergic asthma may be induced by exercise or may be occupational. Between 12 and 15 million persons in the US suffer from asthma. The prevalence in the US increased by 46% between 1982 and 1993 [119].

Children who ate fresh, oily fish more than once per week had a significantly reduced risk of current asthma ($P < 0.01$) [120]. The results of a questionnaire were adjusted for confounders such as atopy, respiratory infection during infancy, and a parental history of asthma or smoking. No other food groups were associated with any risk difference for asthma. In another study [121], 39 asthmatic children were supplemented with omega-3 or omega-6 fatty acids. Large differences were seen in plasma phospholipid fatty acids and TNF-α production was lower than baseline in the omega-3 group. No significant differences were found in clinical outcome measures in this study. Only portions of asthmatic children respond to the treatment with omega-3 fatty acids. Identification of the reasons for different responses is necessary.

Leukotrienes formed from arachidonic acid are involved in the asthma process through vasoconstriction and mucus secretion [122]. Leukotriene synthesis is inhibited by long-chain omega-3 fatty acids [112]. Asthmatic patients were sequentially given a diet with a 10:1 or 2:1 ratio of omega-6 to omega-3 PUFA for 1 month each. The patients were then stressed with methacholine. Methacholine-induced respiratory distress increased with low omega-3 PUFA ingestion. Elevated omega-3 PUFA ingestion gave a positive response with greater than 40% of the patients and the positive response correlated with the increase in the urinary 5-series leukotrienes, the leukotriene made from EPA. Thus, an increased intake of omega-3 fatty acids is beneficial for asthma symptoms for a substantial number of asthma patients [123]. Studies before 1995 had shown little effect on human asthma [124].

IMMUNITY

Pigs were fed diets containing 10.5 wt.% of an oil for 4 weeks before intratracheal inoculation with *Mycoplasma hyopneumoniae*. Lung lesions and peribronchial inflammation were less in pigs fed menhaden oil than in those fed 1:1 mixtures of linseed oil with corn oil or menhaden oil with corn oil. Generally, the gross lung lesions increased as the ratio of omega-3 to omega-6 long-chain fatty acids decreased. These results show that the ratio of omega-3 to omega-6 long-chain fatty acids in the diet may modulate the host response to respiratory infection with less infection associated with a higher level of omega-3 fatty acids from fish oil [125].

Healthy men were given an EPA, DHA, or corn oil supplement for 7 weeks for testing of mononuclear leucocyte function [126]. The quantities of the EPA and DHA supplements were 3.8 and 3.6 g daily, approximately tenfold greater than the recommended intake. Monocytes retained their phagocytic ability and respiratory burst activity after supplementation with an overdose of these long-chain omega-3 fatty acids [126].

FISH OIL

The emphasis on the importance of omega-3 long-chain PUFA has led to the commercial availability of purified fish oil supplements that are available in health food stores. Some consumers do not pay sufficient attention to the recommended dosage and abuse these encapsulated omega-3 supplements. An excessive intake of DHA can disturb membrane permeability and some enzymic activities and also without adequate antioxidant can cause the accumulation of lipid peroxides. The omega-3 to omega-6 ratio of the diet fed to rats was varied using DHA ethyl ester and linoleic acid. The benefits of DHA on lipid metabolism and blood coagulation were seen with ratios of 5:1 and 1.8:1. At ratios of 0.6 or less, negative effects on health benefits were seen [127]. The critical level for safety in rats was at a ratio of 1.8.

The amount of fish now available on world markets is near the maximum possible. This amount increased from approximately 20 million tons in 1950 to approximately 100 million tons in 1990 with no increase since then [128]. In 1992, aquaculture provided an additional 14 million tons. More than 30 million tons, mostly from pelagic fish such as anchovy, sardines, herring and menhaden, was converted to fish meal and fish oil. Fish meal is used for fish feed, 14%; pig feed, 20%; and poultry feed, 58%. Two-thirds of the fish oil is used in human foods and one-third in animal feeds, mostly for fish. Any further increase in aquaculture will require more of the present production of fish meal and fish oil to be diverted from other animal feed or human food, respectively. Farmed fish have optimal growth with fish meal in their diet. Fish oil is required in fish feed because the fatty acids in farmed fish are dependent on their dietary intake and high levels of long-chain omega-3 fatty acids are required for opti-

mal growth. Many freshwater fish can convert LNA to EPA and DHA, but their growth is improved with fish oil in their diet. Farmed fish are generally just as rich in long-chain omega-3 fatty acids as wild fish because they are grown on diets containing fish meal and fish oil. Some varieties, particularly catfish, may contain much lower proportions of long-chain omega-3 fatty acids, because they can be grown more economically with soybean meal and vegetable oils [129].

DHA foods are beneficial because DHA is essential for brain functioning. The inclusion of plentiful DHA in the diet improves learning ability and the development of the brain. DHA is good for the eyes and is helpful in recovery from certain visual dysfunctions. DHA has been reported to prevent and treat senile dementia. DHA has a positive effect on diseases such as hypertension, arthritis, atherosclerosis, depression, diabetes mellitus, myocardial infarction, thrombosis, heart disease, and some cancers.

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