Essential Fatty Acids

- Alpha-linolenic acid (ALA), an omega-3 fatty acid, and linoleic acid (LA), an omega-6 fatty acid, are considered essential fatty acids because they cannot be synthesized by humans.

- The long-chain omega-6 fatty acid, arachidonic acid (AA) can be synthesized from LA.

- The long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can be synthesized from ALA, but EPA and DHA synthesis may be insufficient under certain conditions.

- While DHA appears to be important for visual and neurological development, it is not yet clear whether feeding infants formula enriched with DHA and AA enhances visual acuity or neurological development in preterm or term infants.

- A large body of scientific research suggests that higher dietary omega-3 fatty acid intakes are associated with reductions in cardiovascular disease risk, prompting the American Heart Association to recommend that all adults eat fish, particularly oily fish, at least twice weekly.

- The results of randomized controlled trials indicate that increasing omega-3 fatty acid intake can decrease the risk of myocardial infarction (heart attack) and sudden cardiac death in individuals with coronary heart disease.

- Increasing EPA and DHA intake may be beneficial to individuals with diabetes, especially those with elevated serum triglycerides.

- Randomized controlled trials have found that fish oil supplementation decreases joint tenderness and reduces the requirement for anti-inflammatory medication in rheumatoid arthritis patients.

- Although limited preliminary data suggests that omega-3 fatty acid supplementation may be beneficial in the therapy of depression, bipolar disorder and schizophrenia, larger controlled clinical trials are needed to determine their efficacy.

Omega-3 and omega-6 fatty acids are polyunsaturated fatty acids (PUFA), meaning they contain more than one *cis* double bond. In all omega-3 fatty acids, the first double bond is located between the third and fourth carbon atom counting from the methyl end of the fatty acid (n-3). Similarly, the first double bond in all omega-6 fatty acids is located between the sixth and seventh carbon atom from the methyl end of the fatty acid (n-6). Scientific abbreviations for fatty acids tell the reader something about their structure. One scientific abbreviation for alpha-linolenic acid (ALA) is 18:3n-3. The first part (18:3) tells the reader that ALA is an 18-carbon fatty acid with 3 double bonds, while the second part (n-3) tells the reader that the first double bond is in the n-3 position, which defines it as an omega-3 fatty acid.

Although humans and other mammals can synthesize saturated and some monounsaturated fatty acids from carbon groups in carbohydrate and protein, they lack the enzymes necessary to insert a *cis* double bond at the n-6 or the n-3 position of a fatty acid. Consequently, omega-6 and omega-3 fatty acids are essential nutrients. The parent fatty acid of the omega-6 series is linoleic acid (LA; 18:2n-6) and the parent fatty acid of the omega-3 series is ALA. Humans can synthesize long-chain (20 carbons or more) omega-6 fatty acids, such as dihomo-gamma-linolenic acid (DGLA; 20:3n-6) and arachidonic acid (AA; 20:4n-6) from LA and long-chain omega-3 fatty acids, such as eicosapentaenoic acid (EPA; 20:5n-3) and

docosahexaenoic acid (DHA; 22:6n-3) from ALA. It has been estimated that the ratio of omega-6 to omega-3 fatty acids in the diet of early humans was 1:1, but the ratio in the typical Western diet is now almost 10:1 due to increased use of vegetable oils rich in LA and declining fish consumption. A large body of scientific research suggests that increasing the relative abundance of dietary omega-3 fatty acids may have a number of health benefits.

Metabolism and Bioavailability

Prior to absorption in the small intestine, fatty acids must be hydrolyzed from dietary fats (triglycerides, phospholipids and cholesterol) by pancreatic enzymes. Bile salts must also be present in the small intestine to allow for the incorporation of fatty acids and other fat digestion products into mixed micelles. Fat absorption from mixed micelles occurs throughout the small intestine, and is 85-95% efficient under normal conditions.

Humans can synthesize longer omega-6 and omega-3 fatty acids from the essential fatty acids LA and ALA, respectively, through a series of desaturation (addition of a double bond) and elongation (addition of two carbon atoms) reactions. LA and ALA compete for the same elongase and desaturase enzymes in the synthesis of longer polyunsaturated fatty acids, such as AA and EPA. Although ALA is the preferred substrate of the delta-6 desaturase enzyme, the excess of dietary LA compared to ALA results in greater net formation of AA (20:4n-6) than EPA (20:5n-3).

The capacity for conversion of ALA to DHA is higher in women than men. Studies of ALA metabolism indicate that approximately 8% of dietary ALA is converted to EPA and 0-4% is converted to DHA in healthy young men. In healthy young women, approximately 21% of dietary ALA is converted to EPA and 9% is converted to DHA. The better conversion efficiency of young women compared to men appears to be related to the effects of estrogen.

Although ALA is considered the essential omega-3 fatty acid because it cannot be synthesized by humans, evidence that human conversion of EPA and, particularly, DHA is relatively inefficient suggests that EPA and DHA may also be essential under some conditions.

Biological Activities

Membrane Structure and Function

Omega-6 and omega-3 PUFA are important structural components of cell membranes. When incorporated into phospholipids, they affect cell membrane properties such as fluidity, flexibility, permeability and the activity of membrane bound enzymes. DHA is selectively incorporated into retinal cell membranes and postsynaptic neuronal cell membranes, suggesting it plays important roles in vision and nervous system function.

Vision

DHA is found in very high concentrations in the cell membranes of the retina, which conserves and recycles DHA even when omega-3 fatty acid intake is low. Animal studies indicate that DHA is required for the normal development and function of the retina. Moreover, these studies suggest that there is a critical period during retinal development when inadequate DHA will result in permanent abnormalities in retinal function. Recent research indicates that DHA plays an important role in the regeneration of the visual pigment rhodopsin, which plays a critical role in the visual transduction system that converts light hitting the retina to visual images in the brain.

Nervous System

The phospholipids of brain gray matter contain high proportions of DHA and AA, suggesting they are important to central nervous system function. Brain DHA content may be particularly important, since animal studies have shown that depletion of DHA in the brain

can result in learning deficits. It is not clear how DHA affects brain function, but changes in neuronal cell membrane DHA content could alter the function of ion channels or membrane associated receptors, as well as the availability of neurotransmitters.

Eicosanoid Synthesis

Eicosanoids are potent chemical messengers derived from 20-carbon PUFA that play critical roles in immune and inflammatory responses. During an inflammatory response, DGLA, AA and EPA in cell membranes can be metabolized by enzymes known as cyclooxygenases and lipoxygenases to form prostaglandins and leukotrienes, respectively. In those who consume typical Western diets, the amount of AA in cell membranes is much greater than the amount of EPA, resulting in the formation of more eicosanoids derived from AA than EPA. However, increasing omega-3 fatty acid intake increases the EPA content of cell membranes, resulting in higher proportions of eicosanoids derived from EPA. Physiological responses to AA-derived eicosanoids differ from responses to EPA-derived eicosanoids. In general, eicosanoids derived from EPA are less potent inducers of inflammation, blood vessel constriction, and coagulation than eicosanoids derived from AA.

Regulation of Gene Expression

The results of cell culture and animal studies indicate that omega-6 and omega-3 fatty acids can modulate the expression of a number of genes, including those involved with fatty acid metabolism and inflammation. Although the mechanisms require further clarification, omega-6 and omega-3 fatty acids may regulate gene expression by interacting with specific transcription factors, including peroxisome proliferator-activated receptors (PPARs) and liver X receptors.

Deficiency

Essential Fatty Acid Deficiency

Clinical signs of essential fatty acid deficiency include a dry scaly rash, decreased growth in infants and children, increased susceptibility to infection and poor wound healing. Omega-3, omega-6 and omega-9 fatty acids compete for the same desaturase enzymes. The desaturase enzymes show preference for the different series of fatty acids in the following order: omega-3 > omega-6 > omega-9. Consequently, synthesis of the omega-9 fatty acid eicosatrienoic acid (20:3n-9) increases only when dietary intakes of omega-3 and omega-6 fatty acids are very low. A plasma eicosatrienoic acid:arachidonic acid (triene:tetraene) ratio greater than 0.2 is generally considered indicative of essential fatty acid deficiency. In patients who were given total parenteral nutrition containing fat-free glucose amino acid mixtures, biochemical signs of essential fatty acid deficiency developed in as little as 7-10 days. In these cases, the continuous glucose infusion resulted in high circulating insulin levels, which inhibited the release of essential fatty acids stored in adipose tissue. When glucose-free amino acid solutions were used, parenteral nutrition up to 14 days did not result in biochemical signs of essential fatty acid deficiency. Essential fatty acid deficiency has also been found to occur in patients with chronic fat malabsorption and cystic fibrosis. Recently, it has been proposed that essential fatty acid deficiency may play a role in the pathology of protein energy malnutrition.

Omega-3 Fatty Acid Deficiency

At least one case of isolated omega-3 fatty deficiency has been reported. A young girl who received intravenous lipid emulsions with very little ALA developed visual problems and sensory neuropathy, which resolved when she was switched to an emulsion containing more ALA. Plasma DHA concentrations decrease when omega-3 fatty acid intake is insufficient, but no cutoff values have been established. Isolated omega-3 fatty acid deficiency does not result in increased plasma triene:tetraene ratios.

Disease Prevention

Visual and Neurological Development

Because the last trimester of pregnancy is a critical period for the accumulation of DHA in the brain and retina, preterm infants are thought to be particularly vulnerable to adverse effects of insufficient DHA on visual and neurological development. Human milk contains DHA in addition to ALA and EPA, but until recently, ALA was the only omega-3 fatty acid present in conventional infant formulas. Although preterm infants can synthesize DHA from ALA, they generally cannot synthesize enough to prevent declines in plasma and cellular DHA concentrations without additional dietary intake. Therefore, it was proposed that preterm infant formulas be supplemented with enough DHA to bring plasma and cellular DHA levels of formula-fed infants up to those of breast-fed infants. Although formulas enriched with DHA raise plasma and red blood cell DHA concentrations in preterm and term infants, the results of randomized controlled trials examining measures of visual acuity and neurological development in infants fed formulas with and without added DHA have been mixed. Although several controlled trials found that healthy preterm infants fed formulas with DHA added showed subtle but significant improvements in visual acuity at 2 and 4 months of age compared to those fed DHA-free formulas, most randomized controlled trials found no differences in visual acuity between healthy preterm infants fed formulas with or without DHA added. Similarly, most randomized controlled trials that assessed general measures of infant development at 12 and 24 months of age found no difference between preterm infants fed formula with or without DHA added. Infant formulas enriched with DHA are also commercially available for term infants, but the results of randomized controlled trials of these formulas on visual acuity and development in term infants have also been mixed. While DHA appears to be important for visual and neurological development, it is not yet clear whether feeding infants formula enriched with DHA enhances visual acuity or neurological development in preterm or term infants.

Although infant requirements for DHA have been the subject of a great deal of research, there has been relatively little investigation of maternal requirements for omega-3 fatty acids, despite the fact that the mother is the sole source of omega-3 fatty acids for the fetus and exclusively breast-fed infant. The results of randomized controlled trials during pregnancy suggest that omega-3 fatty acid supplementation does not decrease the incidence of gestational diabetes, pregnancy-induced hypertension or preeclampsia, but may result in modest increases in length of gestation, especially in women with low omega-3 fatty acid consumption. In European women with high risk pregnancies, fish oil supplementation that provided 2.7 g/day of EPA + DHA during the last trimester of pregnancy lowered the risk of premature delivery from 33% to 21%. In healthy Danish women, fish oil supplementation that provided 2.7 g/day of EPA + DHA increased the length of gestation by an average of 4 days. More recently, consumption of only 0.13 g/day of DHA from enriched eggs during the last trimester of pregnancy increased the length of gestation by an average of 6 days in a low-income population in the US. In Norway, children born to mothers who were supplemented with cod liver oil (2 g/day of EPA + DHA) during pregnancy and the first 3 months of lactation scored higher on mental processing tests at 4 years of age when compared to the children whose mothers were not supplemented with cod liver oil. However, only 14% of the original study participants were available for testing when the children were 4 years of age. Although promising, these findings need to be replicated in other studies before it can be concluded that EPA and DHA supplementation during pregnancy has beneficial effects on long-term cognitive development in children.

Cardiovascular Disease

Omega-6 Fatty Acids: Linoleic Acid

LA is the most abundant dietary PUFA. The results of prospective cohort studies examining the relationships between PUFA intake and the risk of coronary heart disease (CHD) have been somewhat

inconsistent. Some, but not all, prospective cohort studies have found that higher PUFA and LA intakes, are associated with significant reductions in CHD risk. The largest prospective cohort study to examine the effects of dietary fat intake on CHD risk is the Nurses' Health Study, which followed more than 78,000 women for 20 years. In that cohort, those with the highest intakes of total PUFA (7.4% of energy) and LA had a risk of CHD that was 25% lower than those with the lowest intakes of total PUFA (5% of energy) and LA. Although saturated fatty acid (SFA) intake was not associated with CHD risk, the ratio of PUFA:SFA intake was inversely associated with CHD risk. In controlled feeding trials, replacing dietary SFA with PUFA consistently lowers serum total and LDL cholesterol concentrations. In fact, LA has been shown to be the most potent fatty acid for lowering serum total and LDL cholesterol when substituted for dietary SFA. Several dietary intervention trials have compared the effects of diets high in SFA (18-19% of energy) with diets low in SFA (8-9% of energy) and high in PUFA (14-21% of energy) on morbidity (illness) and mortality (death) from CHD. Although most of the increase in dietary PUFA was provided by LA, ALA intakes were also increased in these trials. Several dietary intervention trials in men found that replacing dietary SFA with PUFA reduced morbidity or mortality from CHD. However, two similar dietary intervention trials in women did not result in significant reductions in morbidity or mortality from CHD.

Omega-3 Fatty Acids: Alpha-Linolenic Acid

Several prospective cohort studies have examined the relationship between dietary ALA intake and CHD risk. In a cohort of more than 45,000 US men followed for 14 years, each 1-g/day increase in dietary ALA intake was associated with a 16% reduction in the risk of CHD. Moreover, in those who ate little or no seafood, each 1-g/day increase in dietary ALA intake was associated with a 47% reduction in the risk of CHD. In a cohort of more than 76,000 US women followed for 10 years, those with the highest ALA intakes (~1.4 g/day) had a risk of fatal CHD that was 45% lower than women with

the lowest intakes (~0.7 g/day). Interestingly, oil and vinegar salad dressing was an important source of dietary ALA in this population. Women who consumed oil and vinegar salad dressing 5-6 times weekly had a risk of fatal CHD that was 54% lower than those who rarely consumed it, even after adjusting the analysis for vegetable intake. In a smaller cohort of more than 6000 US men, those with the highest intakes of ALA had a risk of death from CHD over the next 10 years that was 40% lower than those with the lowest intakes. In contrast, two studies in Europe found no association between dietary ALA intake and CHD risk. Although not as consistent as the evidence supporting higher intakes of long-chain omega-3 fatty acids from seafood, the results of most prospective studies suggest that higher dietary ALA intakes (2-3 g/day) are associated with significant reductions in CHD risk, especially in populations with low levels of fish consumption. Unlike LA, the cardioprotective effects of higher ALA intakes do not appear to be related to changes in serum lipid profiles. However, several controlled clinical trials found that increasing ALA intake decreased serum concentrations of C-reactive protein (CRP), a marker of inflammation that is strongly associated with the risk of cardiovascular events, such as MI and stroke.

Long-chain Omega-3 Fatty Acids: Eicosapentaenoic Acid and Docosahexaenoic Acid

Evidence is accumulating that increasing intakes of long-chain omega-3 fatty acids (EPA and DHA) can decrease the risk of cardiovascular disease by
1) preventing arrhythmias that can lead to sudden cardiac death
2) decreasing the risk of thrombosis (a clot) that can lead to MI or stroke
3) decreasing serum triglyceride levels
4) slowing the growth of atherosclerotic plaque
5) improving vascular endothelial function
6) lowering blood pressure slightly
7) decreasing inflammation

Coronary Heart Disease:

Several prospective cohort studies have found that men who eat fish at least once weekly have lower mortality from CHD than men who do not eat fish. One such study followed 1822 men for 30 years and found that mortality from CHD was 38% lower in men who consumed an average of at least 35 g (1.2 oz) of fish daily than in men who did not eat fish, while mortality from MI was 67% lower. The cardioprotective effects of fish consumption may not be confined to those consuming a typical Western diet. A study in China that followed more than 18,000 men for 10 years found that those who consumed more than 200 g (~7 oz) of fish or shellfish weekly had a risk of fatal MI that was 59% lower than men who consumed less than 50 grams (~2 oz) weekly. Less information is available regarding the effects of higher omega-3 fatty acid and fish intakes in women. In the Nurses' Health Study, which followed more than 84,000 women for 16 years, CHD mortality was 29-34% lower in women who ate fish at least once a week compared to women who ate fish less than once a month.

Sudden Cardiac Death:

Sudden cardiac death is the result of a fatal ventricular arrhythmia, which usually occurs in people with CHD. Studies in cell culture indicate that long-chain omega-3 fatty acids decrease the excitability of cardiac muscle cells (myocytes) by modulating ion channel conductance. The results of epidemiological studies suggest that regular fish consumption is inversely associated with the risk of sudden cardiac death. In a large prospective cohort study that followed more than 20,000 men for 11 years, those who ate fish at least once a week had a risk of sudden cardiac death that was 52% lower than those who ate fish less than once a month. Plasma levels of EPA and DHA were also inversely related to the risk of sudden cardiac death, supporting the idea that omega-3 fatty acids are at least partially responsible for the beneficial effect of fish consumption on sudden cardiac death. More recently, a prospective study that

followed more than 45,000 men for 14 years found that the risk of sudden cardiac death was about 40-50% lower in those who consumed an average of at least 250 mg/day of dietary EPA + DHA, the equivalent of 1-2 oily fish meals weekly, than those who consumed less than 250 mg/day. Dietary EPA + DHA intake was not related to the risk of nonfatal MI or total CHD events, suggesting the anti-arrhythmic effects of long-chain omega-3 fatty acids may be important at usual dietary intake levels.

Stroke:

Ischemic strokes are the result of insufficient blood flow to an area of the brain, which may occur when an artery supplying the brain becomes occluded by a clot. Hemorrhagic strokes occur when a blood vessel ruptures and bleeds into the brain. In the US, 70-80% of strokes are ischemic strokes. Some prospective studies that have examined the relationship between fish or omega-3 fatty acid intake and total stroke incidence have found increased fish intake to be beneficial, while others found no beneficial effect. More recently, two large prospective studies found that increased fish and omega-3 fatty acid intakes were associated with significantly lower risks of ischemic stroke, but not hemorrhagic stroke. In a study that followed more than 79,000 women for 14 years, those who ate fish at least twice weekly had a risk of thrombotic (ischemic) stroke that was 52% lower than those who ate fish less than once monthly. Similarly, in a study that followed more than 43,000 men for 12 years, those who ate fish at least once monthly had a risk of ischemic stroke that was 43% lower than those who ate fish less than once monthly. Although the effects of long-chain omega-3 fatty acid intake on the incidence of stroke have not been studied as thoroughly as that of CHD, available evidence suggests that increased fish intake may decrease the risk of ischemic stroke, but not hemorrhagic stroke.

Serum Triglycerides:

A meta-analysis of 17 prospective studies found hypertriglyceridemia (serum triglycerides > 200 mg/dl) to be an independent risk factor for cardiovascular disease. Numerous controlled clinical trials in humans have demonstrated that increasing intakes of EPA and DHA significantly lowers serum triglyceride concentrations. The triglyceride-lowering effects of EPA and DHA increase with dose, but clinically meaningful reductions in serum triglyceride concentrations have been demonstrated at doses of 2 g/day of EPA + DHA. In its recommendations regarding omega-3 fatty acids and cardiovascular disease, the American Heart Association indicates that an EPA + DHA supplement may be useful in patients with hypertriglyceridemia.

Summary: Omega-3 and Omega-6 PUFA and Cardiovascular Disease Prevention

The results of epidemiological studies and randomized controlled trials suggest that replacing dietary SFA with omega-6 and omega-3 PUFA lowers LDL cholesterol and decreases cardiovascular disease risk. Additionally, the results of epidemiological studies provide strong evidence that increasing dietary omega-3 fatty intake is associated with significant reductions in cardiovascular disease risk through mechanisms other than lowering LDL cholesterol. In particular, increasing EPA and DHA intake from seafood has been associated with significant reductions in sudden cardiac death, suggesting that long-chain omega-3 fatty acids have anti-arrhythmic effects at intake levels equivalent to the amount in two small servings of oily fish per week.

Disease Treatment

Coronary Heart Disease

Dietary Intervention Trials

Total mortality and fatal MI decreased by 29% in male MI survivors advised to increase their weekly intake of oily fish to 200-400 g (7-14 oz), which was estimated to provide an additional 500-800 mg/day of long-chain omega-3 fatty acids (EPA + DHA). In another dietary intervention trial, patients who survived a first MI were randomly assigned to usual care or advised to adopt a Mediterranean diet that was higher in omega-3 fatty acids (especially ALA) and lower in omega-6 fatty acids than the standard western-style diet. After almost 4 years, those on the Mediterranean diet had a risk of cardiac death and nonfatal MI that was 38% lower than the group that was assigned to usual care. Although higher plasma ALA levels were associated with better outcomes, the benefit of the Mediterranean diet cannot be attributed entirely to increased ALA intakes since intakes of monounsaturated fatty acids and fruits and vegetables also increased.

Supplementation Trials

In the largest randomized controlled trial of supplemental omega-3 fatty acids to date, CHD patients who received supplements providing 850 mg/day of EPA + DHA for 3.5 years had a risk of sudden death that was 45% lower than those who did not take supplements and a risk of death from all causes that was 20% lower. Interestingly, it took only 3 months of supplementation to demonstrate a significant decrease in total mortality and 4 months to demonstrate a significant decrease in sudden death. In another supplementation trial, patients admitted to the hospital with an acute MI were randomized to receive capsules containing fish oil (1.8 g/day of EPA + DHA), mustard oil (2.9 g/day of ALA) or a. After a year, total cardiac events, including nonfatal MI, were significantly lower in the groups that received fish oil or mustard oil compared to the groups that received a placebo. In contrast, acute MI patients did not realize any additional benefit from supplementation with 3.5 g/day of EPA + DHA compared to corn oil in a region of Norway where fish intakes are relatively high. The results of a meta-analysis that pooled the findings of 11 randomized controlled trials of dietary or

supplementary omega-3 fatty acids indicated that increased omega-3 fatty acid intakes significantly decreased overall mortality, mortality due to MI, and sudden cardiac death in patients with CHD.
Two randomized controlled trials have examined the effect of fish oil supplementation on the progression of coronary artery atherosclerosis measured by coronary angiography. Although a study of 59 patients with coronary artery disease found no benefit after two years of supplementation with fish oil providing 6 g/day of EPA +DHA compared to olive oil, a larger trial of 223 patients found that supplementation with 3.3 g/day of EPA + DHA for 3 months and 1.65 g/day for an additional 21 months resulted in a modest decrease in the progression of coronary atherosclerosis compared to a placebo.
Numerous randomized controlled trials have examined the effect of fish oil supplementation on coronary artery restenosis after percutaneous transluminal coronary angioplasty (PTCA). A meta-analysis that combined the results of 12 randomized controlled trials found that fish oil supplementation resulted in a 14% reduction of coronary restenosis, but this reduction did not quite reach statistical significance. Supplemental fish oil doses in the coronary artery restenosis trials ranged from 2.6-6.0 g/day.

Summary

The results of randomized controlled trials in individuals with documented CHD suggest a beneficial effect of dietary and supplemental omega-3 fatty acids. Based on the results of these trials, the American Heart Association recommends that individuals with documented CHD consume approximately 1 g/day of EPA + DHA

Diabetes Mellitus

Cardiovascular diseases are the leading causes of death in individuals with diabetes mellitus (DM). Hypertriglyceridemia (serum triglycerides > 200 mg/dl) is a common lipid abnormality in individuals with type 2 DM, and a number of randomized controlled trials have found that fish oil supplementation significantly lowers

serum triglyceride levels in diabetic individuals. Although early uncontrolled studies raised concerns that fish oil supplementation adversely affected blood glucose (glycemic) control, randomized controlled trials have not generally found adverse effects of fish oil supplementation on long-term glycemic control. A systematic review that pooled the results of 18 randomized controlled trials including more than 800 diabetic patients found that fish oil supplementation significantly lowered serum triglycerides, especially in those with hypertriglyceridemia. A more recent meta-analysis that combined the results of 18 randomized controlled trials in individuals with type 2 DM or metabolic syndrome found that fish oil supplementation decreased serum triglycerides by 31 mg/dl compared to placebo, but had no effect on serum cholesterol, fasting glucose or hemoglobin A1c concentrations. Although few controlled trials have examined the effect of fish oil supplementation on cardiovascular disease outcomes in diabetics, a prospective study that followed 5103 women diagnosed with type 2 DM, but free of cardiovascular disease or cancer at the start of the study, found that higher fish intakes were associated with significantly decreased risks of CHD over a 16-year follow up period. Thus, increasing EPA and DHA intakes may be beneficial to diabetic individuals especially those with elevated serum triglycerides. Moreover, there is little evidence that daily EPA + DHA intakes of less than 3 g/day adversely affect long-term glycemic control in diabetics. The American Diabetes Association recommends that diabetic individuals increase omega-3 fatty acid consumption by consuming two to three 3-oz servings of fish weekly.

Inflammatory Diseases

Rheumatoid Arthritis

Two meta-analyses of randomized controlled trials in rheumatoid arthritis patients found that fish oil supplementation significantly decreased the number of tender joints on physical examination. In general, clinical benefits were observed at a minimum dose of 3 g/day of EPA + DHA, and were not apparent until at least 12 weeks

of supplementation. Neither meta-analysis found that fish oil supplementation had a significant effect on erythrocyte sedimentation rate (ESR), a measure of inflammation. Six out of 7 studies that examined the effect of long-chain omega-3 fatty acid supplementation on nonsteroidal anti-inflammatory drug (NSAID) or corticosteroid use in rheumatoid arthritis patients demonstrated a reduced requirement for anti-inflammatory medication.

Inflammatory Bowel Disease

Clinical trials of long-chain omega-3 fatty acid supplementation have demonstrated beneficial effects less consistently in patients with inflammatory bowel disease than in patients with rheumatoid arthritis. Although two randomized controlled trials of fish oil supplementation in Crohn's disease patients reported no benefit, a significantly higher proportion of Crohn's disease patients supplemented with 2.7 g/day of EPA + DHA remained in remission over a 12-month period than those given a placebo. Three randomized controlled trials of EPA + DHA supplementation (4.2-5.4 g/day for 3-12 months) in ulcerative colitis patients reported significant improvement in at least one outcome measure, including weight gain, decreased corticosteroid use, improved disease activity scores and improved histology scores. In contrast, supplementation of ulcerative colitis patients in remission with 5.1 g/day of EPA + DHA did not significantly alter the incidence of relapse over a 2-year period.

Asthma

Inflammatory eicosanoids (leukotrienes). derived from AA (20:4n-6) are thought to play an important role in the pathology of asthma. Since increasing omega-3 fatty acid intake has been found to decrease the formation of AA-derived leukotrienes, a number of clinical trials have examined the effects of long-chain omega-3 fatty acid supplementation on asthma. Although there is some evidence that omega-3 fatty acid supplementation can decrease the production of

inflammatory mediators in asthmatic patients, evidence that omega-3 fatty acid supplementation decreases the clinical severity of asthma in controlled trials has been inconsistent. Two recent systematic reviews of randomized controlled trials of long-chain omega-3 fatty acid supplementation in asthmatic adults and children found no consistent effects on clinical outcome measures, including pulmonary function tests, asthmatic symptoms, medication use or bronchial hyperreactivity.

Immunoglobulin A Nephropathy

Immunoglobulin A (IgA) nephropathy is a kidney disorder that results from the deposition of IgA in the glomeruli of the kidney. The cause of IgA nephropathy is not clear, but progressive renal failure may eventually develop in 15-40% of patients. Since glomerular IgA deposition results in increased production of inflammatory mediators, omega-3 fatty acid supplementation could potentially modulate the inflammatory response and preserve renal function. In a multicenter randomized controlled trial, supplementation of IgA nephropathy patients with fish oil (1.8 g/day of EPA + 1.2 g/day of DHA) for 2 years significantly slowed declines in renal function. Over the 2-year treatment period, 33% of the placebo group experienced a 50% increase in serum creatinine (evidence of declining renal function) compared to only 6% in the fish oil supplemented group. These results were sustained over an average of 6 years of follow-up, but were not improved with higher doses of fish oil. In contrast, several smaller studies failed to find a significant benefit of fish oil supplementation in IgA nephropathy patients. Interestingly, fish oil treatment (3 g/day of EPA + DHA) for 6 months did not decrease the urinary excretion of inflammatory mediators in IgA nephropathy patients. Two meta-analyses of randomized controlled trials of fish oil supplementation did not find evidence of a statistically significant benefit in IgA nephropathy patients overall. Due to the inconsistent results of available randomized controlled trials, it is not clear whether fish oil supplementation will prevent the progression of IgA nephropathy in children or adults.

Major Depression and Bipolar Disorder

Data from ecological studies across different countries suggest an inverse association between seafood consumption and national rates of major depression and bipolar disorder. Several small studies have found omega-3 fatty acid concentrations to be lower in the plasma and adipose tissue (fat) of individuals suffering from depression compared to controls. Although it is not known how increased omega-3 fatty acid intake affects the incidence of depression, modulation of neuronal signaling pathways and eicosanoid production have been proposed as possible mechanisms. The results of randomized controlled trials of supplementation with long-chain omega-3 fatty acids on depression have been mixed. Adding fish oil supplements (8 g/day) to existing therapy in people who were being treated for depression was not significantly more effective than adding the same amount of olive oil for 12 weeks. Supplementation with 2 g/day of DHA for 6 weeks was not significantly more effective than a placebo in the treatment of major depression. However, a small randomized controlled trial in Chinese patients diagnosed with major depression found that supplementation with 6.6 g/day of EPA + DHA for 8 weeks improved scores on the Hamilton Rating Scale for Depression compared to placebo. Another small randomized controlled trial in 30 women diagnosed with borderline personality disorder found that the 20 women randomized to treatment with 1 g/day of ethyl-EPA for 8 weeks experienced less severe depressive symptoms than the 10 women randomized to treatment with a placebo. Unipolar depression and bipolar disorder are considered distinct psychiatric conditions, although major depression occurs in both. A randomized controlled trial that assessed the effects of high doses of EPA (6.2 g/day) + DHA (3.4 g/day) in patients with bipolar disorder found that those supplemented with EPA + DHA had a significantly longer period of remission than those on an olive oil placebo over a 4-month period. Patients who took the EPA + DHA supplements also experienced less depression than those who took the placebo. Although the results of a few small controlled trials are somewhat optimistic, larger

and long-term randomized controlled trials are required to determine the efficacy of long-chain omega-3 fatty acid supplementation on major depression.

Schizophrenia

Findings of decreased omega-3 fatty acid levels in the red blood cells and brains of a limited number of schizophrenic patients and the results of uncontrolled supplementation studies have created interest in the use of long-chain omega-3 fatty acid supplements as an adjunct to conventional antipsychotic therapy regimens for schizophrenia. A pilot study in 45 schizophrenic patients found that the addition of 2 g/day of EPA to standard antipsychotic therapy was superior to the addition of a 2 g/day of DHA or a placebo in decreasing residual symptoms. When EPA supplementation was used as the sole treatment for schizophrenic patients experiencing a relapse, 8 out of 14 patients supplemented with 2 g/day of EPA required antipsychotic medication by the end of the 12-week study period compared to 12 out of 12 of those on the placebo. Results of randomized controlled trials using ethyl-EPA as an adjunct to standard antipsychotic therapy in schizophrenic patients have been somewhat contradictory. In one trial, the addition of 3 g/day of ethyl-EPA to standard antipsychotic treatment for 12 weeks improved symptom scores and decreased dyskinesia scores, while in a larger trial, supplementation with the same dose of ethyl-EPA was not different than placebo in improving symptoms, mood, or cognition. In a placebo-controlled trial comparing the addition of 1, 2, or 4 g/day of ethyl-EPA to different medication regimens, ethyl-EPA supplementation improved symptoms of schizophrenic patients on the antipsychotic medication clozapine, but not other medications. Although limited evidence suggests that EPA supplementation may be a useful adjunct to antipsychotic therapy in schizophrenic patients, larger long-term studies addressing clinically relevant outcomes are needed.

Food Sources

Omega-6 Fatty Acids

Linoleic Acid: Food sources of LA include vegetable oils, such as soybean, safflower and corn oil, nuts, seeds and some vegetables. Dietary surveys in the US indicate that the average adult intake of LA ranges from 12-17 g/day for men and 9-11 g/day for women. Some foods that are rich in LA are listed in the table below.

Some Food Sources of Linoleic Acid (18:2n-6)		
Food	**Serving**	**Linoleic Acid (g)**
Safflower oil	1 tablespoon	10.1
Sunflower seeds, oil roasted	1 oz	9.7
Pine nuts	1 oz	9.4
Sunflower oil	1 tablespoon	8.9
Corn oil	1 tablespoon	7.2
Soybean oil	1 tablespoon	6.9
Pecans, oil roasted	1 oz	6.4
Brazil nuts	1 oz	5.8
Sesame oil	1 tablespoon	5.6

Arachidonic Acid: Animals, but not plants, can convert LA to AA. Therefore, AA is present in the diet in small amounts in meat, poultry and eggs.

Omega-3 Fatty Acids

Alpha-Linolenic Acid (ALA): Flaxseeds, walnuts, and their oils are among the richest dietary sources of ALA. Canola oil is also an excellent source of ALA. Dietary surveys in the US indicate that average adult intakes for ALA range from 1.2-1.6 g/day for men and from 0.9-1.1 g/day for women. Some foods that are rich in ALA are listed in the table below.

Some Food Sources of Alpha-linolenic Acid (18:3n-3)		
Food	**Serving**	**Alpha-Linolenic acid (g)**
Flaxseed oil	1 tablespoon	8.5
Walnuts, English	1 oz	2.6
Flaxseeds	1 tablespoon	2.2
Walnut oil	1 tablespoon	1.4
Canola oil	1 tablespoon	1.2
Mustard oil	1 tablespoon	0.8
Soybean oil	1 tablespoon	0.9
Walnuts, black	1 oz	0.6
Tofu, firm	½ cup	0.7

Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA): Oily fish are the major dietary source of EPA and DHA. Dietary surveys in the US indicate that average adult intakes of EPA range from 0.04-0.07 g/day and average adult intakes of DHA range from 0.05-0.09 g/day. Omega-3 fatty acid-enriched eggs are also available in the US. Some foods that are rich in EPA and DHA are listed in the table below.

Some Food Sources of EPA (20:5n-3) and DHA (22:6n-3)				
Food	**Serving**	**EPA (g)**	**DHA (g)**	**Amount providing 1 g of EPA + DHA**
Herring, Pacific	3 oz*	1.06	0.75	1.5 oz
Salmon, Chinook	3 oz	0.86	0.62	2 oz
Sardines, Pacific	3 oz	0.45	0.74	2.5 oz
Salmon, Atlantic	3 oz	0.28	0.95	2.5 oz
Oysters, Pacific	3 oz	0.75	0.43	2.5 oz
Salmon, sockeye	3 oz	0.45	0.60	3 oz

Trout, rainbow	3 oz	0.40	0.44	3.5 oz
Tuna, canned, white	3 oz	0.20	0.54	4 oz
Crab, Dungeness	3 oz	0.24	0.10	9 oz
Tuna, canned, light	3 oz	0.04	0.19	12 oz

*A 3-oz serving of fish is about the size of a deck of cards.

Biosynthesis of EPA and DHA
Humans can synthesize AA from LA and EPA and DHA from ALA through a series of desaturation and elongation reactions.

Supplements

Omega-6 Fatty Acids

Borage seed oil, evening primrose oil and black currant seed oil are rich in gamma-linolenic acid (GLA), and are often marketed as GLA or essential fatty acid (EFA) supplements.

Omega-3 Fatty Acids

Flaxseed oil (also known as flax oil or linseed oil) is available as an ALA supplement. A number of fish oils are marketed as omega-3 fatty acid supplements. Ethyl esters of EPA and DHA (ethyl-EPA and ethyl-DHA) are concentrated sources of long-chain omega-3 fatty acids. Since EPA and DHA content will vary in fish oil and ethyl ester preparations, it is necessary to read the label to determine the EPA and DHA content of a particular supplement. DHA supplements derived from algal and fungal sources are also available. All omega-3 fatty acid supplements are absorbed more efficiently with meals. Dividing one's daily dose into two or three smaller doses throughout the day will decrease the risk of gastrointestinal side effects. Cod liver oil is a rich source of EPA and DHA, but some cod liver oil preparations may contain excessive amounts of preformed vitamin A (retinol).

Infant Formula

In 2001, the FDA began permitting the addition of DHA and AA to infant formula in the US. Presently, manufacturers are not required to list the amounts of DHA and AA added to infant formula on the label. However, most infant formula manufacturers provide this information. The amounts added to formulas in the US range from 8-17 mg DHA/100 calories (5 fl oz) and from 16-34 mg AA/100 calories. For example, an infant drinking 20 fl oz of DHA-enriched formula daily would receive 32-68 mg/day of DHA and 64-136 mg/day of AA.

Safety -- Adverse Effects

Gamma-Linolenic Acid (18:3n-6)

Supplemental gamma-linolenic acid is generally well-tolerated, and serious adverse side effects have not been observed at doses up to 2.8 g/day for 12 months. High doses of borage seed oil, evening primrose oil or black currant seed oil may cause gastrointestinal upset, loose stools or diarrhea. Because of case reports that supplementation with evening primrose oil induced seizure activity in people with undiagnosed temporal lobe epilepsy, people with a history of seizures or seizure disorder are generally advised to avoid evening primrose oil and other gamma-linolenic acid-rich oils.

Alpha-Linolenic Acid (18:3n-3)

Although flaxseed oil is generally well tolerated, high doses may cause loose stools or diarrhea. Allergic and anaphylactic reactions have been reported with flaxseed and flaxseed oil ingestion.

Eicosapentaenoic Acid (20:5n-3) and Docosahexaenoic Acid (22:6n-3)

Serious adverse reactions have not been reported in those using fish oil or other EPA and DHA supplements. The most common adverse effect of fish oil or EPA and DHA supplements is a fishy aftertaste. Belching and heartburn have also been reported. High doses may cause nausea and loose stools.

Potential for Excessive Bleeding: The potential for high omega-3 fatty acid intakes, especially EPA and DHA, to prolong bleeding times has been well studied, and may play a role in the cardioprotective effects of omega-3 fatty acids. Although excessively long bleeding times and increased incidence of hemorrhagic stroke have been observed in Greenland Eskimos with very high intakes of EPA + DHA (6.5 g/day), it is not known whether high intakes of EPA and DHA are the only factor responsible for these observations. The US FDA has ruled that intakes up to 3 g/day of long-chain omega-3 fatty acids (EPA and DHA) are Generally Recognized As Safe (GRAS) for inclusion in the diet, and available evidence suggests that intakes less than 3 g/day are unlikely to result in clinically significant bleeding. Although the Institute of Medicine did not establish a tolerable upper level of intake (UL) for omega-3 fatty acids, caution was advised with the use of supplemental EPA and DHA, especially in those who are at increased risk of excessive bleeding.

Potential for Immune System Suppression: Although the suppression of inflammatory responses resulting from increased omega-3 fatty acid intakes may benefit individuals with inflammatory or autoimmune diseases, anti-inflammatory doses of omega-3 fatty acids could decrease the potential of the immune system to destroy pathogens. Studies comparing measures of immune cell function outside the body (ex vivo) at baseline and after supplementing people with omega-3 fatty acids, mainly EPA and DHA, have demonstrated immunosuppressive effects at doses as low as 0.9 g/day for EPA and 0.6 g/day for DHA. Although it is not clear if these findings translate to impaired immune responses in vivo, caution should be observed

when considering omega-3 fatty acid supplementation in individuals with compromised immune systems.

Infant Formula

In early studies of DHA-enriched infant formula, EPA- and DHA-rich fish oil was used as a source of DHA. However, some preterm infants receiving fish oil-enriched formula had decreased plasma AA concentrations, which were associated with decreased growth. This effect was attributed to the potential for high concentrations of EPA to interfere with the synthesis of AA, which is essential for normal growth. Consequently, EPA was removed and AA was added to DHA-enriched formula. Currently available infant formulas in the US contain only AA and DHA derived from algal or fungal sources, rather than fish oil. Randomized controlled trials have not found any adverse effects on growth in infants fed formulas enriched with AA and DHA for up to one year.

Pregnancy and Lactation

The safety of supplemental omega-3 and omega-6 fatty acids, including borage seed oil, evening primrose oil, black currant seed oil and flaxseed oil has not been established in pregnant or lactating (breastfeeding) women. Studies of fish oil supplementation during pregnancy and lactation have not reported any serious adverse effects

Contaminants in Fish

Some species of fish may contain significant levels of methylmercury, polychlorinated biphenyls (PCBs) or other environmental contaminants. In general, larger predatory fish, such as swordfish, tend to contain the highest levels of these contaminants. Removing the skin, fat and internal organs of the fish prior to cooking, and allowing the fat to drain from the fish while it cooks will decrease exposure to a number of fat-soluble pollutants, such as PCBs. However, methylmercury is found throughout the muscle of fish, so

these cooking precautions will not reduce exposure to methylmercury. Organic mercury compounds are toxic and excessive exposure can cause brain and kidney damage. Unborn children, infants, and young children are especially vulnerable to the toxic effects of mercury on the brain. In order to limit their exposure to methylmercury, the US Department of Health and Human Services (DHHS) and Environmental Protection Agency (EPA) have made the following joint recommendations for women who may become pregnant, pregnant women and breastfeeding women:

1) Do not eat shark, swordfish, king mackerel and tile fish (also known as golden bass or golden snapper) because they contain high methylmercury levels.

2) Eat up to 12 oz (2 average meals) per week of a variety of fish that are lower in mercury.
a) The five most commonly consumed fish that are low in mercury include canned light tuna, shrimp, salmon, catfish and pollock.
b) Limit the consumption of canned white (albacore) tuna and tuna steak to 6 oz (one average meal) per week.
3) Check local advisories regarding the safety of fish caught by friends or family in local lakes, rivers and coastal areas.
When feeding fish to young children, the DHHS and EPA advise following the above guidelines but serving smaller portions, such as 3 oz, for an average meal.

For more information about the FDA/EPA consumer advisory on methylmercury in fish, see their online brochure. More information about mercury levels in commercial fish and shellfish is available from the FDA.

Contaminants in Supplements

Although concerns have been raised regarding the potential for omega-3 fatty acid supplements derived from fish oil to contain methylmercury, PCBs and dioxins, several independent laboratory analyses in the US have found commercially available omega-3 fatty

acid supplements to be free of methylmercury, PCBs and dioxins. The absence of methylmercury in omega-3 fatty acid supplements can be explained by the fact that mercury accumulates in the muscle, rather than the fat of fish. In general, fish body oils contain lower levels of PCBs and other fat-soluble contaminants than fish liver oils. Additionally, fish oils that have been more highly refined and deodorized also contain lower levels of PCBs. Pyrrolizidine alkaloids, potentially hepatotoxic and carcinogenic compounds, are found in various parts of the borage plant. People who take borage oil supplements should use products that are certified free of pyrrolizidine alkaloids.

Drug Interactions

Gamma-linolenic acid supplements, such as evening primrose oil or borage seed oil, may increase the risk of seizures in people on phenothiazines, such as chlorpromazine. High doses of black currant seed oil, borage seed oil, evening primrose oil, flaxseed oil and fish oil may inhibit platelet aggregation, and should be used with caution in people on anticoagulant medications. In particular, people taking fish oil or long-chain omega-3 fatty acid (EPA and DHA) supplements in combination with anticoagulant drugs, including aspirin, clopidogrel (Plavix), dalteparin (Fragmin), dipyridamole (Persantine), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid) and warfarin (Coumadin), should have their coagulation status monitored using a standardized prothrombin time assay (INR). One small study found that 3 g/day or 6 g/day of fish oil did not affect INR values in 10 patients on warfarin over a 4-week period. However, a recent case report described an individual who required a reduction of her warfarin dose when she doubled her fish oil dose from 1 g/day to 2 g/day.

Nutrient Interactions

Vitamin E

Outside the body, PUFA become rancid (oxidized) more easily than SFA. Fat-soluble antioxidants, such as vitamin E, play an important role in preventing the oxidation of PUFA. Inside the body, results of animal studies and limited data in humans suggest that the amount of vitamin E required to prevent lipid peroxidation increases with the amount of PUFA consumed. One widely used recommendation for vitamin E intake is 0.6 mg of alpha-tocopherol per g of dietary PUFA. This recommendation was based on a small study in men and the ratio of alpha-tocopherol to LA in the US diet, and has not been verified in more comprehensive studies. Although EPA and DHA are easily oxidized outside the body, it is presently unclear whether EPA and DHA are more susceptible to oxidative damage within the body. High vitamin E intakes have not been found to decrease biomarkers of oxidative damage when EPA and DHA intakes are increased, but some experts believe that an increase in PUFA intake, particularly omega-3 PUFA intake, should be accompanied by an increase in vitamin E intake.

Intake Recommendations

US Institute of Medicine

In 2002, the Food and Nutrition Board of the US Institute of Medicine established adequate intake (AI) levels for omega-6 and omega-3 fatty acids, which are listed in the tables below.

Adequate Intake (AI) for Omega-6 Fatty Acids				
Life Stage	**Age**	**Source**	**Males (g/day)**	**Females (g/day)**
Infants	0-6 months	Omega-6 PUFA*	4.4	4.4
Infants	7-12 months	Omega-6 PUFA*	4.6	4.6
Children	1-3 years	LA#	7	7
Children	4-8 years	LA	10	10

Children	9-13 years	LA	12	10
Adolescents	14-18 years	LA	16	11
Adults	19-50 years	LA	17	12
Adults	51 years and older	LA	14	11
Pregnancy	All ages	LA	-	13
Lactation	All ages	LA	-	13

*The various omega-6 polyunsaturated fatty acids (PUFA) present in human milk can contribute to the AI for infants. # LA, linoleic acid

Adequate Intake (AI) for Omega-3 Fatty Acids				
Life Stage	**Age**	**Source**	**Males (g/day)**	**Females (g/day)**
Infants	0-6 months	ALA, EPA, DHA*	0.5	0.5
Infants	7-12 months	ALA, EPA, DHA	0.5	0.5
Children	1-3 years	ALA	0.7	0.7
Children	4-8 years	ALA	0.9	0.9
Children	9-13 years	ALA	1.2	1.0
Adolescents	14-18 years	ALA	1.6	1.1
Adults	19 years and older	ALA	1.6	1.1
Pregnancy	All ages	ALA	-	1.4
Lactation	All ages	ALA	-	1.3

*All omega-3 polyunsaturated fatty acids present in human milk can contribute to the AI for infants. ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

International Recommendations

The European Commission recommends an omega-6 fatty acid intake of 4-8% of energy and an omega-3 fatty acid intake of 2 g/day of ALA and 200 mg/day of long-chain omega-3 fatty acids (EPA and DHA). The World Health Organization recommends an omega-6 fatty acid intake of 5-8% of energy and an omega-3 fatty acid intake of 1-2% of energy. However, the Japan Society for Lipid Nutrition has recommended that LA intake be reduced to 3-4% of energy in Japanese people whose omega-3 fatty acid intakes average 2.6 g/day, including about 1 g/day of EPA + DHA.

American Heart Association

The American Heart Association recommends that people without documented CHD eat a variety of fish (preferably oily) at least twice weekly, in addition to consuming oils and foods rich in ALA. People with documented CHD are advised to consume approximately 1 g/day of EPA + DHA preferably from oily fish, or to consider EPA + DHA supplements in consultation with a physician. Patients who need to lower serum triglycerides may take 2-4 g/day of EPA + DHA supplements under a physician's care.