

## Omega-3 Fatty Acids and Psychiatric Disorders

### Biochemistry

The essential fatty acids

There are two distinct classes of essential fatty acids (EFAs), omega-6 (n-6) and omega-3 (n-3). The abbreviations, n-3 and n-6 (also called omega-3 and omega-6) refer to the position of the first double bond when counting from the end of the chain opposite the carboxyl group. The EFAs are essential because they cannot be synthesized, but must be ingested in foods or as dietary supplements. The n-3 and n-6 EFAs are not interconvertible in humans. These two classes are distinct and have opposing physiological functions. The essential nature of the fatty acids, linoleic (LA, 18:2n-6) and alpha-linolenic (LNA, 18:3n-3), has been known since 1929 ([Burr, 2000](#)). These 18-carbon fatty acids are required for synthesis of the longer polyunsaturated fatty acids (PUFAs), such as arachidonic acid (20:4n-6 or AA) and eicosapentaenoic acid (EPA or 20:5n-3). The later 20-carbon PUFAs are precursors of eicosanoids which have pervasive physiological activities. The 18 carbon n-3 fatty acids are found in plants such as flax seed, while the longer chained (EPA and DHA [docosahexaenoic acid, 22:6n-3]) are found primarily in marine sources, especially fatty fish (salmon, tuna, mackerel) ([Kris-Etherton et al., 2000](#)). ALA is not converted very well to EPA and DHA even in healthy humans. Is it likely that susceptibility to many of the pathological conditions to be described here are due to a diminished ability to elongate and desaturate these 18 carbon chains.

#### *Figure 1: EFA-Pathways*

PUFAs play a critical role in determining lipid-protein interactions in synaptic neuronal membranes which affect receptor conformation, ion channels, enzymes, and the movement of compounds into and out of the cell (Salem, 1989). Neuronal membranes contain high concentrations of DHA and AA; both of these EFAs are crucial components of the phospholipid bilayer. Each of these fatty acids comprises approximately 25% of the phospholipid content (Mahadik and Evans, 1997). Neurotransmitter receptors lie embedded within the matrix of this membrane and their 3-dimensional conformation is dependant on the specific fatty acids that give structure to the membrane (Mitchell et al., 1998).

While both n-6 and n-3 EFAs are essential for health, the balance of the two is critical. Diets that provide n-6 oils at the expense of n-3 will stimulate production of *pro-inflammatory* prostaglandins, while n-3's stimulate *anti-inflammatory* prostaglandins. The n-6 and n-3 fatty acids influence eicosanoid metabolism, gene expression, and intercellular communication (eicosanoids include prostaglandins, cytokines, cytokine mediators, and other components of the immune response). Balance between the two fatty acids is critical because they compete with one another for synthetic enzymes and have many opposite metabolic functions via their metabolism to their respective eicosanoids (Fig. 1). An inadequately opposed n-6 pathway can create a physiological situation that promotes chronic inflammation, and propagation of cancer, heart disease, stroke, diabetes, arthritis, auto-immunity and impaired neuronal functioning – including mental disorders ([Connor, 2000](#); [James et al., 2000](#); [Kremer, 2000](#)). EFAs are critical components of practically all cell membranes. There will likely be an imbalance between n-6-based eicosanoids and n-3-based eicosanoids if there is a significant imbalance in dietary EFA precursors. The PUFA composition of neuronal membranes is, to a great extent, dependent on dietary intake.

While a balance of EFAs may be as important than absolute amounts, recent changes in dietary fat ingestion are having deleterious health consequences (Simopoulos, 1999). Studies indicate that a high intake of n-6 fatty acids shifts the physiologic state to one that is more prothrombotic and proaggregatory. This is characterized by increases in blood viscosity, vasospasm, vasoconstriction and decreases in bleeding time. N-3 fatty acids, however, have anti-inflammatory, antithrombotic, antiarrhythmic, hypolipidemic, and vasodilatory properties. Highly unsaturated fatty acids, especially n-3 fatty acids, have antiatherogenic properties via modulation of endothelial activation ([De Caterina et al., 2000](#)). Physiological functions of the EFAs include the control of inflammation, cardiovascular health, myelin sheath development, allergic reactivity, immune response, hormone modulation, cognition, and behavior. These beneficial effects of n-3 fatty acids have been shown in the secondary prevention of coronary heart disease, hypertension, type 2 diabetes mellitus, rheumatoid arthritis, ulcerative colitis, Crohn's disease, and chronic obstructive pulmonary disease (Simopoulos, 1999; 2000; [Belluzzi et al., 2000](#), [Connor, 2000](#); [von Schacky, 2000](#); [Nestel, 2000](#) ; [Dewailley et al., 2002](#); [Hu et al., 2002](#)).

*Figure: Simopoulos*

Prior to the twentieth century, humans ingested an approximately equal proportion (1/1 ratio) of n-6 to n-3 essential fatty acids (EFAs). Today the ratio may be as high as 20 or 25:1 of n-6:n-3. These historical diets were less dense in calories and richer in high fiber fruits and vegetables, lean meat, and fish. They also had higher levels of the longer-chain PUFAs, such as EPA, DHA, and AA. Today's diet places a greater burden on the body's need to synthesize long-chain PUFAs from 18-carbon EFAs (Simopoulos, 2000; [Kris-Etherton et al., 2000](#)).

Figure 4 (from Simopoulos, 1999)

The industrial revolution, over the past 100-150 years, resulted in an enormous increase in the consumption of n-6 fatty acids due to the increased intake of vegetable oils from corn, sunflower seeds, safflower seeds, cottonseed, and soybeans. These oils are not only high in n-6 but relatively devoid of the complementary n-3 fatty acids. In addition, methods for fattening cattle and chickens more quickly for slaughter have resulted in the feeding of n-6 containing grains. This results in meat and eggs with very low n-3 content compared to free-range livestock. Food manufacturers learned that n-3 significantly decreases the shelf-life (since it is easily oxidized) and therefore the profitability of processed foods, so sources of n-3 are purposely avoided. An excess of n-6 EFAs can suppress the synthesis of long-chain n-3 PUFAs such as EPA and DHA. These natural PUFAs have in fact been replaced by trans-fatty acids which are not easily oxidized and do not become rancid. While they taste and "feel" like real fats, they are handled very differently and inhibit the enzymes that are involved with desaturation and elongation of the 18-carbon PUFAs to the 20 and 22-carbon long-chain (LC)PUFAs (Ascherio and Willett, 1997). The formation of LCPUFAs also depends on adequate amounts of zinc as a cofactor for several desaturase enzymes along the formation pathways. Thus, there are at least three major factors limiting the synthesis of n-3 LCPUFAs: excessive n-6 EFAs, introduced trans-fatty acids, and zinc deficiency. The conversion of 18-carbon n-3, linoleic acid, to the 20-carbon EPA is not an efficient process, only about 0.2% is converted ([Salem et al., 1999](#); [Pawlosky et al., 2001](#)).

## **DHA**

DHA is highly concentrated in, and is critical for the proper functioning of central nervous system tissues (particularly synaptic membranes) and retinal rod outer segments. DHA deficiencies during

pre- and postnatal development are believed to adversely affect visual acuity, cognitive capabilities, and possibly behavioral and psychiatric disorders ([Fugh-Berman and Cott, 1999](#)). Studies with nonhuman primates and human newborns indicate that DHA is essential for the normal functional development of the retina and brain ([Birch et al., 2000](#); [SanGiovanni et al., 2000](#); [Birch et al., 2002](#); [Neuringer, 2000](#); [Carlson, 2000](#); [Champoux et al., 2002](#)). DHA is taken up by the brain in preference to other fatty acids and the turnover in the brain is very fast (Horrocks and Yeo, 1999; [Rapoport et al., 2001](#)). Preformed sources of DHA and AA are required since production from their precursors is inadequate to support the developmental needs of infants ([Salem et al., 1995](#)). It has been suggested that humans developed large brains only because of the availability of preformed n-3 from marine sources ([Crawford et al., 1999](#); [Richards et al., 2001](#)).

Although a recommended dietary allowance for essential fatty acids does not exist, an adequate intake (AI) has been estimated for n-6 and n-3 essential fatty acids by an international scientific working group ([Simopoulos et al., 1999](#); Simopoulos, 2000). For Western societies, it will be necessary to decrease the intake of n-6 fatty acids and increase the intake of n-3 fatty acids.

## **Mechanism**

Non-esterified fatty acids released from membrane lipids belong to a large group of eicosanoids affecting hormones and growth factors which control the shift between cell multiplication and differentiation. The EFAs act on this shift by influencing, as second messengers or modulators, the interrelated mechanisms of action of growth factors and steroid hormones ([Nunez, 1997](#)).

Both lithium and valproic acid are known to inhibit protein kinase C (PKC) activity after subchronic administration in cell culture and in vivo ([Chen et al. 1999](#); [2000](#)). [Seung et al. \(2001\)](#) determined the effects of the n-3 fatty acids EPA and DHA on PKC phosphotransferase activity in vitro. Both DHA and EPA, as well as the combination, inhibited PKC activity at concentrations as low as 10 micromol/L, while AA had no effect. Thus, PKC inhibition represents a potential mechanism for n-3 fatty acids in the treatment of bipolar disorder.

Earlier studies suggested that n-3 fatty acids inhibited cAMP-dependent protein kinase (PKC) activity in intact cells. This led [Mirnikjoo et al. \(2001\)](#) to report that n-3 fatty acids inhibited the in vitro activities of PKC, Ca(2+)/calmodulin-dependent protein kinase II, and 5-HT-induced activation of the mitogen-activated protein kinase (MAPK). Results from both in vitro and live cell preparations suggested that inhibition of second messenger-regulated protein kinases is a potential mechanism of action of n-3 fatty acids ([Mirnikjoo et al., 2001](#)).

N-3 fatty acids appear to be useful in conditions in which the pathophysiology involves overactivity of second messenger systems. For example, they exert anti-inflammatory action in animal models of lupus and rheumatoid arthritis and show significant amelioration of autoimmune disorders ([Kelley et al., 1985](#); [Leslie et al., 1985](#); [Reddy Avula et al., 2002](#); [Venkatraman and Meksawan, 2002](#); [Gruenwald et al., 2002](#); [Ergas et al., 2002](#)). Biochemical studies have shown that high-dose therapy with omega-3 fatty acids leads to the incorporation of these compounds into the membrane phospholipids crucial for cell signaling ([Schiefermeier and Yavin, 2002](#)), and suppresses phosphatidylinositol-associated second messenger activity (similar to the proposed actions of lithium and valproate).

The antimanic drugs, lithium and valproic acid, have a common mechanism reported recently in rats (Rapoport and Bosetti, 2002). Animals fed lithium chloride to produce a brain lithium concentration of 0.7mM, reduced AA turnover within brain phospholipids by 75%. The effect was highly selective since turnover rates of DHA and palmitic acid were unaffected. AA turnover in rat brain also was reduced by long-term valproic acid administration. Lithium's reduction of AA turnover corresponded to its down-regulating of phospholipase A2 (PLA2), an enzyme that selectively cleaves AA but not DHA from phospholipids. Lithium also reduced the brain activity of cyclooxygenase 2, and the concentration of prostaglandin E(2), an AA metabolite resulting from the action of cyclooxygenase 2. The authors suggest that the antimanic properties of lithium and valproate may be related to this dampening of the "arachidonic acid cascade," which may be overactive in mania (Rapoport and Bosetti, 2002). Since n-3 fatty acids act in opposition to many of the effects of AA, this could be another common mechanism with other mood stabilizing drugs.

DHA also has a protective role in cell culture models of apoptosis through by increasing cellular phosphatidylserine (PS); also, the loss of DHA leads to a loss in PS. Thus, DHA may play an important role in the regulation of cell signaling and in cell proliferation through its effects on PS ([Salem et al., 2001](#)).

### **Essential Fatty Acids and Disease**

The concept of the link between various disease states and n-3 fatty acid deficiency is at least 20 years old (Rudin, 1981; 1982). A comparison was drawn between pellagra and beriberi – once major causes of different mental disorders – schizophreniform, manic-depressive-like, and phobic neurotic, plus drying dermatoses, autonomic neuropathies, tinnitus, and fatigue. He suggested the n-3 fatty acids provide the substrate upon which niacin and other B vitamins act to form the prostaglandin 3 series. Rudin reported that all of these mental diseases exhibit similar pellagra and beriberi-like physical disorders and that they are ameliorated with supplements of the, then, newly discovered n-3 essential fatty acid from flax seed oil.

Horrocks and Yeo (1999) suggest that (in addition to the mental disorders discussed below) DHA deficiencies are associated with fetal alcohol syndrome, cystic fibrosis, phenylketonuria, and adrenoleukodystrophy. A recent review suggests major health benefits in many disease categories ([Connor, 2000](#)). Six of ten prospective cohort studies have reported an inverse relationship between fish intake and cardiovascular disease mortality ([Albert et al., 1998](#)). Epidemiological studies have shown a strong correlation between fish consumption and reduction in sudden death from myocardial infarction (Marchioli et al., 2002; Albert et al., 2002; Bucher et al., 2002). Not only does fish oil reduce triglycerides in the blood and decrease thrombosis, but it also prevents cardiac arrhythmias ([Kang and Leaf, 2000](#)). Nearly 20 years ago, the relationship between low mortality rate from coronary heart disease, and high consumption of seafood was established. Now, the association of n-3 deficiency with depression may be the basis for the robust positive correlation between depression and myocardial infarction (Severus et al., 2001). In fact many of the disorders connected with EFA deficiency are also correlated with depression. Prognosis is generally worse when these pathologies are associated with depression ([Horrobin and Bennett, 1999a](#)).

The relevance to psychiatry is compellingly presented in the recent book, *Phospholipid Spectrum Disorder in Psychiatry* (Peet et al., 1999). A genetic component in these "phospholipid spectrum disorders" is very likely. While no specific genes have been identified, many of the chromosomal

regions identified contain genes that code for enzymes involved in fatty acid and phospholipid metabolism ([Horrobin and Bennett, 1999b](#); [Bennett and Horrobin, 2000](#)).

### **Fatty acid oxidation**

Of particular relevance to mental disorders may be the sensitivity of the PUFAs to destruction by peroxidation. The odor of old fish is largely the result of oxidation of the n-3 PUFAs. There is evidence that free radicals are involved in neuronal membrane pathology, particularly in schizophrenia. Free radicals are reactive chemical species generated during normal metabolic processes, and, in excess, can damage lipids, proteins, and DNA. Areas with high oxygen consumption, high PUFA content, and transition metals (such as neuronal synaptic membranes) are especially vulnerable. Excessive free radicals are also associated with alcohol, tobacco, excessive caloric intake, and physical and psychic stress. Elaborate antioxidant defense systems exist to protect against oxidative stress. They consist of enzymatic (superoxide dismutase, glutathione peroxidase, and catalase) and non-enzymatic (urate, glutathione, zinc, vitamins A, C, and E,  $\beta$ -carotene, and trace elements) systems. In mental disorders, particularly schizophrenia, there is evidence for an inadequacy of these defense systems. This may lead to a dysregulation of free radical metabolism, as determined by abnormal activities of critical antioxidant enzymes and other markers of lipid peroxidation in plasma, red blood cells, and cerebrospinal fluid. These abnormalities have been associated with tardive dyskinesia, negative symptoms, neurological signs, poor premorbid function, and CT scan abnormalities (Reddy and Yao, 1966; Mahadik and Scheffer, 1996; Mahadik et al., 2001).

### **Pregnancy**

The human brain and the retina of the eye consist largely of fatty tissue characterized by long-chain polyunsaturates. In addition to providing energy, the fatty acids in our diet provide important building blocks for the brain and the retina of the eye. In utero, the placenta selectively and substantially extracts AA and DHA from the mother and transfers them to the fetal circulation ([Crawford, 2000](#)). The mother is dependent on her EFAs from the diet ([Al et al., 1995](#); [2000](#)). To optimize the development of the foetus and the infant, it is critical to ensure a sufficient intake of n-3 fatty acids, especially during the last trimester of pregnancy and the first six months after birth. To accomplish this, most mothers-to-be need to include at least the n-3 fatty acids in their diet during their pregnancy and breast-feeding period ([Matorras et al., 2001](#); Hibbeln, 2002). A vegetarian diet may even exacerbate a relative deficiency of n-3 fatty acids, creating a sub-optimum nutritional state during pregnancy (Sanders, 1999). Supplementation of n-3 PUFAs during pregnancy increases n-3 content of breast milk and umbilical plasma phospholipids ([Helland et al., 2001](#)). Freeman (2000) suggests that n-3 fatty acids may prove to be a safe and efficacious treatment for psychiatric disorders in pregnancy and in breastfeeding.

A study (Olsen et al., 1991) suggested that the type of fatty acids in the diet may influence the length of gestation. In the Faeroe Islands, women deliver their babies after the customary 9 months of gestation while a high percentage of women in other parts of Denmark go into labor almost a week earlier. The difference was thought to be a result of the marine diet eaten on the Faeroes. These investigators hypothesized that a high intake of marine-derived n-3 fatty acids might prolong pregnancy by shifting the balance of production of prostaglandins involved in parturition.

In a clinical trial, Olsen et al. (1992) tested the effects of a fish-oil supplement on pregnancy duration, birthweight, and birth length. 533 healthy Danish women in week 30 of pregnancy were

randomized to a fish-oil supplement (containing 2.7 g n-3 fatty acids per day), control (four 1 g olive-oil capsules per day), or no supplementation. At the end of this study, the mean length of gestation differed by ANOVA ( $p = 0.006$ ). It was longest in the fish-oil group and lowest in the olive-oil group. The result was similar when the analysis was limited to women ( $n=443$ ) who underwent early ultrasound estimates of gestational age. Pregnancies in the fish-oil group were on average 4.0 (95% confidence interval 1.5-6.4) days longer than those in the olive-oil group and the birthweight was 107 (1-214) g greater. The difference between the fish-oil and the other groups was increased by a low fish intake at baseline. Thus, fish-oil supplementation in the third trimester seems to prolong pregnancy without detrimental effects on the growth of the fetus or on the course of labor.

While a difference of four days in term deliveries may be of little clinical significance, fish oil may be helpful in preventing recurrent preterm birth. In a recent study (Olsen et al., 2000), the preventive effects of dietary n-3 fatty acids on preterm delivery and several other outcomes were examined. Four prophylactic trials included 232 women with a previous preterm delivery who were randomized to 2.7 g n-3 fatty acids/day or olive oil placebo, starting from about 20 weeks. Fish oil reduced the risk of preterm delivery from 33% to 21% (odds ratio 0.54).

Finally, a prospective cohort study in Denmark, 8729 pregnant women reported that the occurrence of preterm delivery differed significantly across four groups of seafood intake, falling progressively from 7.1% in the group never consuming fish to 1.9% in the group consuming fish at least once a week ([Olsen and Secher, 2002](#)).

In addition to reducing the incidence of preterm births, dietary n-3 may reduce the incidence of cerebral palsy ([Petridou et al., 1998](#)).

### **Postpartum Depression**

Postpartum depression is defined in the DSM-IV as a major depressive episode that occurring within one month of delivery, but the literature reflects broader definitions including periods of up to one year postpartum. Estimates of the prevalence of postpartum depression range from 10% to 20% of women after delivery, and risk factors include previous personal histories of postpartum depression and major depressive episodes ([Pariser, 1993](#); [Altshuler et al., 1998](#)); between 25% and 50% of mothers with postpartum depression have episodes lasting 6 months or longer ([Beck, 2002](#)). Women with postpartum depression are more likely than the nonpostpartum women to present with anxious features, take longer to respond to pharmacotherapy, and require more antidepressant agents at the time of response to treatment ([Hendrick et al., 2000](#)). Pharmacological intervention during gestation and lactation may carry risks for the baby. While these numbers seem bad enough, there is the impression that the incidence of postpartum depression is increasing in Western countries, with the afflicted mothers acting out in ever more violent ways see [British Medical Journal](#) and ([Regan and Alderson, 2002](#)).

The physiology of pregnancy involves the mobilization of polyunsaturated fatty acids from maternal stores to the fetus, and supplementation with essential fatty acids may ensure adequate supplies for the needs of the mother and the developing fetus. Hornstra et al. (1995) demonstrated that maternal essential fatty acids, especially the DHA proportion, progressively decrease during pregnancy. Without sufficient dietary intake, mothers become depleted of DHA, and depletion of maternal n-3 fatty acids has been noted during pregnancy (Otto et al., 1997). Lactation may

increase the period needed for DHA to return to normal levels ([Otto et al., 2001](#)). Multiple births exacerbate the DHA deficiency ([Al et al., 2000](#)). Maternal DHA can be reduced by 50% during pregnancy and not fully restored at 6 months postpartum ([Holman et al., 1991](#); [Al et al., 1995](#)). Mothers selectively transfer DHA via a placental membrane fatty acid-binding protein to their fetuses to enable optimal neurological development during pregnancy (Campbell et al., 1998; [Dutta-Roy, 2000](#); [Martin et al., 2000](#)). [<sup>3</sup>H]DHA accumulates in nerve growth cones during perinatal development, is primarily esterified in phosphatidylethanolamine, is neuroprotective, and significantly reduces PLA2 activity ([Martin, 1998](#)). During pregnancy, the placenta pumps DHA from the expectant mother to the fetus, increasing the mother's susceptibility to depression. Thus it is possible that brain levels also are low during late pregnancy and the early postpartum period and that this maternal DHA depletion may contribute to postpartum depression.

Maternal diet influences the level of DHA in breast milk. The DHA content of mother's milk in the United States is among the lowest in the world. Daily dietary intake of DHA is about 40-50 mg in US women, 200 mg in European women, and about 600 mg in Japanese women. The DHA content of mothers' breast milk is a biological marker for maternal n-3 fatty acid status in postpartum women ([Al et al., 1995](#); [Makrides et al., 1996](#)). The high incidence of postpartum depression in the United States may be triggered by a low dietary intake of DHA. The higher the intake of DHA, the lower the incidence of depression. A 1998 study by Joseph Hibbeln of the National Institute of Alcohol and Alcohol Abuse of the NIH, found a significant inverse correlation between DHA intake and incidence of clinical depression ([Hibbeln, 1998](#)).

A more recent study by Hibbeln found the same relationship between DHA levels in breast milk and incidence of postpartum depression ([Hibbeln, 2002](#)). The published prevalence data for postpartum depression was examined in a study that used 14,532 subjects in 41 studies. These data were compared to the DHA, EPA and AA content in mothers' milk and to seafood consumption rates in published reports from 23 countries. Both higher concentrations of DHA in mothers' milk ( $r=-0.84$ ,  $p<0.0001$ ,  $n=16$  countries) and greater seafood consumption ( $r=-0.81$ ,  $p<0.0001$ ,  $n=22$  countries) predicted lower prevalence rates of postpartum depression ([Hibbeln, 2002](#)). The AA and EPA content of mothers' milk were unrelated to depression prevalence. Interventional studies are desperately needed to determine if n-3 fatty acids can reduce or eliminate postpartum depressive symptoms.

### **Infants and n-3 fatty acids**

A number of studies suggest a positive association between breastfeeding and cognitive development in childhood. A prospective longitudinal birth cohort study was conducted in 973 men and women and a sample of 2280 men, all of whom were born in Copenhagen, Denmark, between October 1959 and December 1961 ([Mortensen et al., 2002](#)). The samples were divided into 5 categories based on duration of breastfeeding. Duration of breastfeeding was associated with significantly higher scores on the Verbal, Performance, and Full Scale WAIS IQs. After regression adjustment for potential confounding factors, the mean Full Scale WAIS IQs were 99.4, 101.7, 102.3, 106.0, and 104.0 for breastfeeding durations of less than 1 month, 2 to 3 months, 4 to 6 months, 7 to 9 months, and more than 9 months, respectively ( $P = .003$  for overall F test). The authors speculated that the n-3 fatty acids in breast milk might be responsible for these differences ([Mortensen et al., 2002](#)).

Breast milk, unlike infant formula, has relatively high concentrations of DHA and EPA (Salem, 1989). The World Health Organization recommends that DHA and EPA be added to infant formulas. Although human breast milk contains DHA and AA, infant formulas marketed in the United States have been virtually devoid of these nutrients. European infant formulas are routinely fortified with these fatty acids. In June of 2001, the FDA finally approved the addition of AA and DHA to infant formula and fortified products are starting to appear in the marketplace. These n-3 fatty acids are crucial for the optimal development of the fetal and neonatal brain and nervous system ([Holman et al., 1991](#)). Intellectual development may also suffer in infants deprived of these fatty acids. A recent study found that infants who's formula was supplemented with long chain PUFAs during their first 4 months performed better at 10 months of age on a problem-solving test than infants given the unsupplemented formula (Willatts et al., 1998). Another study found that sleep patterns of infants born to mothers with higher plasma phospholipid DHA suggest greater CNS maturity ([Cheruka et al., 2002](#)).

In previously depleted, newborn rats, addition of DHA and AA to the diet reversed all deficits (lipid composition of cerebral membranes and dopaminergic neurotransmission) if given during the lactating period but not if given after weaning ([Kodas et al., 2002](#)). Another report, however, found that behavioral deficits in rats involving reduced levels of catecholamines were reversible after weaning by supplementing with DHA ([Takeuchi et al., 2002](#)). Recent neurochemical evidence provides additional links for effects of n-3 deficiency on behavior. The mesolimbic dopamine pathway is more active whereas the mesocortical pathway is less active in n-3 deficient rats than in control rats ([Zimmer et al., 2002](#)). FA imbalance as well as specific FA deficiencies can adversely affect development, such as the ability to respond to environmental stimulation. Dietary n-3 FA deficiency influences specific neurotransmitter systems, particularly the dopamine systems of the frontal cortex. For example, dietary deficiency of n-3 FA impaired the performance of rats on delayed matching-to-place in the water maze, a task associated with prefrontal dopamine function ([Wainwright, 2002](#)).

The effects of dietary DHA supplied during infancy on later cognitive development of healthy term infants were evaluated in a randomized clinical trial of infant formula milk supplemented with 0.35% DHA or with 0.36% DHA and 0.72% AA, or control formula which provided no DHA or AA ([Birch et al., 2000](#)). Fifty-six 18-month-old children (26 male, 30 female) who were enrolled in the trial within the first 5 days of life and fed the assigned diet to 17 weeks of age were tested using the Bayley Scales of Infant Development, 2nd edition (BSID-II). Supplementation of infant formula with DHA+AA was associated with a mean increase of 7 points on the Mental Development Index (MDI) of the BSID-II. Both the cognitive and motor subscales of the MDI showed a significant developmental age advantage for DHA- and DHA+AA-supplemented groups over the control group. While a similar trend was found for the language subscale, it did not reach statistical significance. Significant correlations between plasma and RBC-DHA at 4 months of age but not at 12 months of age and MDI at 18 months of age suggest that early dietary supply of DHA was a major dietary determinant of improved performance on the MDI.

The explanation for these results given by the authors is that n-3 fatty acids, DHA in particular, are absorbed into brain cells during the later stage of pregnancy and the first period after birth, and that they are a prerequisite for normal brain development. The importance of DHA for normal brain development has already been documented by earlier studies on premature babies, but this has now been shown to be relevant for babies born at full term.

A randomized, controlled clinical trial was performed supplementing long-chain polyunsaturated fatty acids (LCPUFA) in 65 healthy term infants who were weaned from breast-feeding at 6 weeks of age ([Birch et al., 2002](#)). This was to determine if the dietary supply of LCPUFAs after weaning influenced the maturation of visual acuity and stereo acuity. Despite a dietary supply of LCPUFAs from breast milk during the first 6 weeks of life, infants who were weaned to formula without LCPUFAs had significantly poorer visual acuity at 17, 26, and 52 weeks of age and significantly poorer stereo acuity at 17 weeks of age than infants who were weaned to LCPUFA-supplemented formula. Better acuity and stereo acuity at 17 weeks was correlated with higher concentrations of DHA in plasma. Better acuity at 52 weeks was correlated with higher concentrations of DHA in plasma and red blood cells ([Birch et al., 2002](#)).

## Children and Adolescents

Deficiencies or imbalances in n-3 and n-6 essential fatty acids may contribute to both the predisposition and the developmental expression of dyslexia, dyspraxia, ADHD and autism ([Richardson and Ross, 2000](#); [Richardson and Puri, 2000](#)). Fatty acid abnormalities help to account for some of the key cognitive and behavioral features of these childhood conditions and their accompanying visual, motor, attentional or language processing disorders. They may also play a part in some of the associated difficulties with mood, appetite or digestion, temperature regulation and sleep ([Richardson and Puri, 2000](#); [Taylor and Richardson, 2000](#)).

The necessity of these unique lipids for brain and behavioral development has received considerable attention over the last 50 years (Wainwright, 1992). Dietary fats clearly affect the levels of cholesterol, phospholipids, and sphingomyelin in brain microsomal and synaptosomal membranes (Foot et al., 1982). Changes in membrane composition resulting from the diet take place rapidly, and appear to be continuously modified according to the lipids consumed (Innis and Clandinin, 1981).

Deficiencies in HUFAs lead to physical signs including excessive thirst, frequent urination, dry scaly skin, and behavioral abnormalities. Noting that these signs were common in hyperactive children, [Colquhoun and Bunday \(1981\)](#) pioneered the theory that HUFA deficiencies could underlie the behavioral problems in ADHD. They suggested that this could account for the apparent intolerance shown by many ADHD children to foods containing salicylates. Since salicylates impair the cyclo-oxygenase pathway for converting HUFA into eicosanoids, they could thus exacerbate any problems resulting from low levels of EPA or AA. They also noted the frequency of atopic conditions and zinc deficiency in ADHD and the fact that non-affected siblings consumed similar diets.

Mitchell et al., (1987) measured plasma fatty acids in 44 hyperactive children and 45 matched control subjects, and found the hyperactive children had significantly lower concentrations of DHA, AA, and the AA precursor DGLA. Stevens and her collaborators at Indiana University measured plasma and red cell fatty acid levels in 53 boys with ADHD and 43 controls, aged 6-12 years. Symptoms associated with fatty acid deficiency were found in 40% of them. They confirmed the lowered plasma concentrations of DHA and AA (but not of DGLA); and found plasma EPA and RBC AA was decreased ([Stevens et al., 1995](#)). A greater number of behavior and sleep problems, temper tantrums, and learning and health problems were found in subjects with lower total n-3 fatty acid concentrations ([Stevens et al., 1996](#)).

Clinical symptoms of fatty acid deficiency were determined in 97 dyslexic children. Children with greater fatty acid deficiencies showed poorer reading ( $P < 0.02$ ) and lower general ability ( $P < 0.04$ ) than children with few such clinical signs. The relationships were stronger among the 72 males and were also associated with poorer spelling and auditory working memory ([Richardson et al., 2000a](#)).

Signs of fatty acid deficiency were significantly elevated in dyslexic subjects relative to controls, particularly males ( $P < 0.001$ ). The severity of the clinical signs of fatty acid deficiency was strongly correlated with the severity of dyslexic symptoms not only in the visual domain, but also with respect to auditory, linguistic and motor problems ([Taylor et al., 2000](#)).

[Stordy \(2000\)](#) correlated the symptoms with n-3 deficiencies and learning disabilities. These deficiencies did not appear to be totally dependent on dietary intakes. There may be innate metabolic deficiencies that result in reduced ability to form and store these fats. Lower plasma levels of LC-PUFA may reflect a relative deficiency of these fatty acids throughout the body. If deficiencies were found in the brain, the resulting membrane structural changes that would occur could well underlie the abnormal behaviors shown by children with ADHD.

[Burgess et al. \(2000\)](#) have reported that children having these lipid deficiencies had significantly more behavioral problems, temper tantrums, and learning, health, and sleep problems than did those children who did not. While the reasons for the lower proportions of LCPUFAs in these children are not clear, factors involving fatty acid intake, conversion of EFAs to LCPUFA and to phospholipids products, and enhanced breakdown of these lipids may relate to the behavioral disturbances.

A recent report showed children and adolescents with ADHD to have reduced brain volumes ([Castellanos et al., 2002](#)). Perhaps the missing volume could be accounted for by deficiencies in essential fatty acids? While no prevention studies exist for ADHD, the reasonable conclusion would be to provide adequate phospholipids to the diet of children with the aim of preventing nutritional deficiencies.

In autistic spectrum subjects, recent findings indicate an even greater indication of these physical signs of fatty acid deficiency as well as reduced levels of n-3 HUFAs in red cell membranes ([Bell et al., 2000](#)). These studies have also suggested that membrane HUFAs from autistic subjects appear to be especially vulnerable to breakdown during storage unless the samples are kept at extremely low temperatures. Preliminary evidence indicates that this may reflect an excess of a PLA2 enzyme that removes HUFAs from phospholipid membranes. High levels of this enzyme have previously been reported in both schizophrenia and dyslexia ([MacDonell et al., 2000](#)), and in dyslexic adults, abnormal membrane lipid turnover was also suggested by the results of brain imaging with 31-phosphorus magnetic resonance spectroscopy ([Richardson et al., 1997](#)).

Treatment studies with essential fatty acids have been extremely difficult due to the wide range of behavioral disturbances included within each diagnostic category. Unless subjects can be pre-selected by reliable objective measures of fatty acid status, decisions on the best kind of treatment to use are difficult. By their very nature, randomised controlled trials do not allow treatments to be individually tailored, and for evaluating mental health treatments they have additional limitations ([Slade and Priebe, 2001](#)). Only a few such studies of fatty acid supplementation in these developmental disorders have been reported. Two early studies showed very marginal results with the n-6, gamma-linolenic acid, in ADHD (Aman et al., 1987; Arnold et

al., 1989), but more recent work has focused on abnormalities of, and supplementation with, n-3 oils.

Sixty-three 6- to-12-year-old children with ADHD, all receiving maintenance therapy with stimulant medication, were randomly assigned to receive double-blind DHA supplementation (345 mg/day) or placebo for 4 months ([Voigt et al., 2001](#)). At the end of the study, plasma DHA content of the DHA-supplemented group was 2.6 times higher than the placebo group ( $P < .001$ ), however, there was no statistically significant improvement in any objective or subjective measure of ADHD symptoms.

The first randomized controlled trial involving dyslexic children examined 41 children aged 8-12 years with both specific learning difficulties and above-average ADHD ratings. They were randomly assigned to receive fatty acid supplementation or placebo. After 12 weeks treatment, mean scores for cognitive problems and general behavior problems were significantly lower for the group treated with FA than for the placebo group; there were significant improvements from baseline on 7 out of 14 scales for active treatment, compared with none for placebo. Thus, supplementation with fish oil and evening primrose oil (providing mainly n-3 but some n-6) can reduce behavioral and learning problems in those with ADHD tendencies ([Richardson and Puri, 2002](#)).

Fetal life and infancy are particularly critical periods for nervous tissue development. Therefore, with respect to human nutrition, adequate amounts of essential fatty acids should be provided during pregnancy, lactation and infancy, and probably throughout life (Connor and Neuringer, 1988).

### *Hostility*

In a recent study, forty-one students took either DHA-rich oil capsules containing 1.5-1.8 g DHA/day (17 females and 5 males) or control oil capsules containing 97% soybean oil plus 3% fish oil (12 females and 7 males) for 3 months. They took a psychological test measuring hostility at the start and end of the study. In the control group, hostility measured by test Study was significantly increased at the end of the study (during exams) as compared with that measured at the start (+58%), whereas it was not significantly changed in the DHA group (-14%) (Hamazaki et al., 2000).

In a similar study, 42 students took either the DHA-rich capsules (1.5-1.8 g DHA/day) or control capsules for 3 months (starting at the end of summer vacation and ending just before the final exams). In the control group, external aggression (aggression against others) was significantly increased at the end of the study as compared with that measured at the start (+8.9%), whereas it was not significantly changed in the DHA group (-1.0%). In a companion double-blind study, the investigators measured external aggression under nonstressful conditions. There were no differences between the two groups under these conditions (Hamazaki et al., 1999).

In another study, the investigators determined whether DHA intake modified the plasma catecholamines and cortisol levels during stress. Control subjects (4 males and 3 females) took 10 control capsules/day and those in the DHA group (4 males and 3 females) took 10 DHA capsules/day containing 1.5 g DHA for 9 weeks, during which subjects underwent more than 20 stressful final exams. At the start and end of the study, plasma catecholamines (epinephrine,

norepinephrine (NE) and dopamine) and cortisol (indicators of stress) were measured. NE concentrations were significantly reduced after DHA administration (-31%,  $p < 0.03$ ). The other catecholamines and cortisol did not change significantly. The plasma ratio of epinephrine to NE increased in every DHA subject (+78%,  $p < 0.02$ ), and intergroup differences were significant ( $p < 0.03$ ). The authors concluded that the effects of DHA may be applied to people under long-lasting psychological stress to prevent stress-related diseases (Sawazaki et al., 1999).

There is evidence that prisoners consume diets lacking in essential nutrients and this could adversely affect their behavior. Gesch et al. (2002) tested to determine if physiologically adequate intakes of vitamins, minerals and essential fatty acids could reduce antisocial behavior in a double-blind, placebo-controlled, randomized trial. Disciplinary offences before and during nutritional supplementation were measured in 231 young adult prisoners. Those receiving active treatment committed an average of 26.3% fewer offences ( $P=0.03$ ) compared with placebos.

## **Omega-3 and Mood**

### *Depression*

It has been suggested that depletion of n-3 PUFAs, particularly DHA, impairs membrane function and may be of etiological importance in depression, and other mental and neurological disorders (Hibbeln et al., 1989; Hibbeln and Salem, 1995; Hillbrand et al., 1997; Hibbeln et al., 1997; [Fugh-Berman and Cott, 1999](#)). Adequate long-chain polyunsaturated fatty acids, particularly DHA, may reduce the development of depression just as they may reduce coronary artery disease. There appears to be an inverse relationship between the prevalence of major depression and the amount of fish consumed per capita worldwide (Hibbeln, 1998). The strong association between depression and heart disease can be explained in part by deficiencies of n-3 fatty acids (Severus et al., 2001).

There is intriguing indirect evidence to support the possibility that lowered blood levels of certain fats may result in behavioral disturbances. Rapid lowering of blood lipids by HMG-CoA reductase inhibitors is associated with a large number of psychiatric disorders; 15% of psychiatric drug reactions were attributed to statins in a national Norwegian database (Buajordet et al., 1997). Reactions included aggression, nervousness, depression, anxiety, and sleeping disorders. Additional data are accumulating that suggest an association between PUFAs and the “mood” neurotransmitter, serotonin. Severely depressed patients have lower levels of the serotonin metabolite, 5-HIAA, in CSF. Both cholesterol lowering therapies and low cholesterol levels have been associated with an increased risk of suicide (Muldoon et al., 1990; Neaton et al., 1992; Golomb, 1998). It has been proposed that low cholesterol levels lower serotonin turnover, however, drug and diet therapies that lower cholesterol also lower essential fatty acid levels. Since essential fatty acid levels predict CSF 5-HIAA levels, and cholesterol does not (Hibbeln et al., 1998a; Hibbeln et al., 1998b; [Hibbeln et al., 2000](#)) cholesterol levels may be a surrogate marker for changes in essential fatty acids.

Geographic areas where consumption of DHA is high are associated with decreased rates of depression. DHA deficiency states, such as alcoholism and the postpartum period, also are linked with depression. Individuals with major depression have marked depletions in n-3 FAs (especially DHA) in erythrocyte phospholipids compared with controls. These data suggest that DHA may be associated with depression.

Patients with major depression have an increased ratio of AA to EPA in their plasma (Maes et al., 1996; [Adams et al., 1996](#)) and erythrocytes (Maes et al., 1996; Edwards et al., 1998; [Adams et al., 1996](#)). It was recently reported that fatty acid composition of phospholipid in erythrocyte membranes (thought to mirror neuronal membranes) of depressive patients showed significant depletions of total n-3 PUFA, particularly DHA (Peet et al., 1998). The limited data available on supplementation with DHA or other n-3 FAs support the hypothesis that EFAs may have antidepressant effects (Mischoulon and Fava, 2000).

Depression is associated with an increased n-6/n-3 ratio and decreases in n-3 fractions in plasma or in the red blood cell membrane. Maes et al. (1999) reported that major depression was associated with a decreased oxidative potential index; significant positive correlations between serum Zn and EPA and DHA fractions in phospholipids; and significant inverse correlations between serum Zn and n-6 fatty acids in phospholipids. There was no significant effect of antidepressive treatment on any of the FAs. The results show that in major depression there is a deficiency of n-3 PUFAs and a compensatory increase in monounsaturated fatty acids and C22:5n-6 in phospholipids. This suggests an abnormal metabolism of n-3 PUFAs in depression; the depression may be related to an inflammatory response; and the lipid disorders may persist despite successful antidepressant treatment (Maes et al., 1999).

In a sample of 3,204 Finnish adults, depressive symptoms were estimated with the Beck Depression Inventory, and a frequency question was used to approximate n-3 fatty acid intake as measured by fish consumption. Multiple logistic regression analysis (adjusted for potential confounders) found the likelihood of having depressive symptoms was significantly higher among infrequent fish consumers than among frequent consumers (Tanskanen et al., 2001).

Mischoulon and Fava (2000) suggest that natural medications may be best for treating mild to moderate illness. Based on the data available to them in 2000, they propose that the role of DHA as a therapy for minor and subsyndromal depression and as an adjunct to standard therapy in more severely depressed patients.

The benefits of EPA as an adjunct in a single patient with depression was recently reported ([Puri et al., 2001](#); [Puri et al., 2002](#)). EPA was added to the conventional antidepressant treatment in a treatment-resistant severely depressed and suicidal male patient with a seven-year history of unremitting depressive symptoms. The addition of the ethyl ester of EPA (E-EPA, Laxdale Research, Ltd.) resulted in a marked and sustained clinical improvement in all the symptoms of depression, within one month. During the nine-month period, the relative concentration of cerebral phosphomonoesters increased by 53%, and the ratio of cerebral phosphomonoesters to phosphodiester increased by 79%, indicating reduced neuronal phospholipid turnover. Imaging showed that the EPA treatment was accompanied by structural brain changes including, in particular, a reduction in the lateral ventricular volume.

Nemets et al. (2002) studied the purified n-3 fatty acid, E-EPA, as an adjunct to treatment for depressive episodes in patients with recurrent unipolar depression. Twenty patients (17 F, 3 M) participated in a 4-week, parallel-group, double-blind addition of either placebo or E-EPA together with their ongoing antidepressant therapy. Significant benefits of the EPA compared with placebo were seen by week 3 of treatment (Figure X).

*(Nemets Figure)*

In another recent study with E-EPA, 70 patients with persistent depression despite ongoing treatment with conventional antidepressant drugs were enrolled (Peet and Horrobin, 2002). Patients were assessed using the 17-item Hamilton Depression Rating Scale, the Montgomery-Åsberg Depression Rating Scale, and the Beck Depression Inventory. In a randomized, double-blind, 12 week trial, they received either E-EPA (1, 2, or 4 g/day) or placebo in addition to conventional antidepressant medication. Forty-six (88%) of 52 patients receiving E-EPA and 14 (78%) of 18 patients receiving placebo completed the study with no serious adverse effects. Patients who received 1 g/day significantly improved on all three scales in measures of depression compared with placebo, but those receiving 2 g/day did not. The group receiving 4 g/day showed a nonsignificant trend toward improvement.

*(Figure from Peet and Horrobin, 2002)*

### **Bipolar Disorder**

Bipolar Disorder (manic-depressive illness) is a common neuropsychiatric illness with a high morbidity and mortality. Despite available mood-stabilizing drugs, including lithium and valproate, there are high rates of recurrence. All of the currently available mood-stabilizing drugs appear to inhibit neuronal signal transduction (or second messenger) systems, supporting the hypothesis that overactive cell-signaling pathways are involved in the pathological process underlying bipolar disorder (Stoll et al., 1996; Berridge et al., 1982; Chen et al., 1994; [1999](#); [2000](#); Manji et al., 1996). Biochemical studies have shown that high-dose therapy with n-3 fatty acids leads to the incorporation of these compounds into the membrane phospholipids crucial for cell signaling (Medini et al., 1990; Sperling et al., 1993; [Schiefermeier and Yavin, 2002](#)). Phosphatidylinositol-associated second messenger activity is also suppressed. This mechanism is similar to the putative actions of lithium and valproate (Kinsella, 1990). The ingestion of large amounts of n-3 fatty acids is associated with a general dampening of signal transduction pathways associated with phosphatidylinositol, AA, and other systems (Sperling et al., 1993; Tappia et al., 1997).

A recent study by Andrew Stoll et al. (1999) showed that dietary supplementation with DHA and EPA showed marked mood-stabilizing activity in bipolar disorder. A 4-month, double-blind, placebo-controlled study compared 15 one-gram capsules of fish oil daily (containing 9.6 g/day n-3 fatty acids) to an olive oil placebo, as an adjunct to usual treatment in 30 patients with bipolar disorder. Participating subjects were men and women, 18 to 65 years old, who met DSM-IV criteria for bipolar disorder (types I or II), and were free of other medical and psychiatric illnesses. Patients were required to have had at least 1 manic or hypomanic episode within the past year, in order to enhance the power of the study to detect a difference between the two treatment groups within the study period. Forty percent of the study cohort had rapid-cycling symptoms, defined as 4 or more mood episodes in the year before enrollment in the study. Patients were permitted to continue with their outpatient psychiatrist or psychotherapist, but no new psychotherapeutic or pharmaceutical interventions were permitted. Subjects receiving other medications at entry continued to receive these medications at constant dosages (whether or not they were considered to be in the therapeutic range).

The 15 patients receiving 15 g daily of fish oil had mild dose-related gastrointestinal distress (nausea and loose stools) as the primary complaint. Also, “fishy” breath was occasionally noted. The n-3 fatty acid-treated group had a significantly longer period of remission than the placebo group ( $P=.002$ ); during the 4-month trial, 2 of 14 patients relapsed in the fish oil group while 9 of 16 relapsed in the placebo-treated group. Significant group differences in favor of fish oil were

seen on the Hamilton depression scale, the Global Assessment Scale and the Clinical Global Impression. No differences were seen on the Young Mania Rating Scale. The authors concluded that n-3 fatty acids were well tolerated and improved the short-term course of illness in this preliminary study of patients with bipolar disorder.

## **Schizophrenia**

There is increasing evidence that oxidative stress injury contributes to the pathophysiology of schizophrenia, as indicated by increased lipid peroxidation products in plasma and CSF, and altered levels of antioxidants in chronic and drug-naive first-episode schizophrenic patients (Mahadik and Mukherjee, 1996; Mukerjee et al., 1996; Mahadik et al., 1998; Mahadik et al., 2001; Khan et al., 2002). An increase of plasma lipid peroxidation is also consistent with lower levels of polyunsaturated essential fatty acids of erythrocyte plasma membrane phospholipids (Rotrosen and Wolkin, 1987) as well as in the brain (Horrobin et al., 1991). AA and DHA levels are relatively depleted in the RBC membranes of chronic schizophrenic patients, compared to normal controls (Peet et al., 1996).

Oxidative stress can lead to global cellular peroxidation that is more evident in neuronal membranes since neurons are enriched in highly susceptible lipids. Because membrane phospholipids play a critical role in neuronal signal transduction, oxidative damage of these lipids may contribute to the proposed altered neurotransmitter receptor-mediated signal transduction and thereby alter information processing in schizophrenia. This neuronal peroxidation may affect its function (i.e., membrane transport, loss of mitochondrial energy production, gene expression and therefore receptor-mediated phospholipid-dependent signal transduction).

These pathologies may explain the altered information processing in schizophrenia (Mahadik et al., 2001). Considerable effort has been directed towards determining the respective roles of increased oxidative stress (increased breakdown) versus dietary deficiencies or defective metabolic pathways (reduced synthesis) on membrane fatty acid concentrations (Mahadik and Evans, 1997). This depletion is believed by others to result from an increased breakdown of these fatty acids rather than by impaired incorporation into membranes (Peet et al., 1995). In any case, several strategies have been proposed by Mahadik et al. (2001) to reduce these effects:

Oxidative neuronal injury can be prevented by dietary supplementation of antioxidants (e.g., vitamins E, C and A; beta-carotene, Q-enzyme, flavons, etc.) and membrane phospholipids can be corrected by dietary supplementation with essential fatty acids.

In addition, oxidative stress may be lower in populations consuming a lower caloric diet and minimizing smoking and drinking (patients in developed countries show higher levels of lipid peroxidation and lower levels of membrane phospholipids as compared to patients in the developing countries).

The life style of schizophrenic patients is also pro-oxidative stress, i.e., heavy smoking, drinking, high caloric intake with no physical activity and treatment with pro-oxidant drugs.

The administration of E-EPA to a drug-naive patient with schizophrenia led to a dramatic and sustained clinical improvement in both positive and negative symptoms ([Richardson et al., 2000b](#)). This was accompanied by a normalization of n-3 and n-6 fatty acids in erythrocyte membranes, in

particular, EPA appears to have reversed the depletion of not only n-3 FAs, but also of membrane AA, possibly by inhibition of phospholipase A(2), or by activation of a fatty acid coenzyme A ligase ([Richardson et al., 2000b](#)). The recovery of this patient was also associated with reduced neuronal membrane phospholipid turnover, as evidenced by serial <sup>31</sup>-phosphorus cerebral MRI ([Puri et al., 2000](#)). Motor laterality also appeared to be altered as a strong right-hand preference became nearly symmetrical due to a marked improvement in his left-hand scores ([Richardson et al., 1999](#)).

In an uncontrolled study with 20 chronic patients (showing primarily negative symptoms), dietary supplementation for six weeks with 10 g per day of fish oil (MaxEPA) led to significant improvement in negative (alogia, flat affect, anhedonia, apathy, motor retardation) but not positive symptoms (hallucinations, disorganized thought) as rated by the Positive and Negative Syndrome Scale (PANSS). Improvement in clinical symptoms was related to increased levels of n-3 fatty acids in RBC (Laugharne et al., 1996).

Since erythrocyte membrane phospholipid composition appears to reflect that of neuronal membranes, PUFA concentrations were measured in the erythrocyte membranes of 19, consecutively admitted, medicated young schizophrenic patients and then compared with matched control subjects (Assies et al., 2001). Psychiatric symptomatology was rated with the Positive and Negative Symptom Scale (PANS) and Montgomery-Åsberg Depression Rating Scale. Diet, hormones, and cannabis use was included in the study since these factors influence fatty acid metabolism. C22:5 n-3 and DHA were significantly decreased, but AA was not. The total n-9 fatty acid levels were also lower in patients. The differences were not due to diet or hormonal status and could not be explained by medication or cannabis use (Assies et al., 2001).

A recent randomized, parallel-group, double-blind, placebo-controlled, fixed-dose, 12-week study investigated the efficacy and tolerability of E-EPA as add-on treatment in chronic, severe schizophrenia (Emsley et al., 2002). Forty patients with persistent symptoms after at least 6 months of stable antipsychotic treatment received E-EPA or placebo, in addition to their existing treatment. At 12 weeks, the E-EPA group had significantly greater reduction of PANS total scores and of dyskinesia scores than the placebo group. EPA may be an effective and well-tolerated add-on treatment in schizophrenia (Emsley et al., 2002).

In a similar study, [Peet and Horrobin \(2002\)](#) tested the effects of E-EPA on persistent ongoing symptoms in patients receiving different types of anti-schizophrenic drugs, typical antipsychotics, new atypical antipsychotics, and clozapine. 115 patients with DSM-IV-defined schizophrenia were studied, 31 on clozapine, 48 on new atypical drugs, and 36 on typical antipsychotics. Placebo or 1, 2 or 4 g/day of E-EPA was given for 12 weeks in addition to the ongoing medication. Patients on 2 and 4 g/day E-EPA showed significant reductions in triglyceride levels which had been elevated by clozapine. In patients given 2 g/day E-EPA there were improvements on the PANSS and its sub-scales, but there was also a large placebo effect in patients on typical and new atypical antipsychotics and no difference were seen between active treatment and placebo. On the other hand, patients on clozapine experienced little placebo response, and a clinically relevant and statistically significant effect of E-EPA was seen on all rating scales. The effect was greatest at 2 g/day. There was a positive relationship between improvement on rating scales and increase in RBC AA concentration ([Peet and Horrobin, 2002](#)).

Initial observations suggest an improved outcome in schizophrenia in patients supplemented with essential fatty acids and antioxidants. It is conceivable that dietary supplementation with antioxidants (e.g. vitamins E and C, beta-carotene) and n-3 fatty acids at the initial stages of illness

may prevent further oxidative injury and thereby ameliorate and prevent further possible deterioration of associated neurological and behavioral deficits in schizophrenia (Mahadik and Scheffer, 1996). Since the oxidative stress exists at or before the onset of psychosis, the use of antioxidants early on may reduce the oxidative injury and dramatically improve the outcome of illness (Mahadik et al., 2001).

## **Dementia**

(Conquer et al., 2000) Fatty acid differences, including docosahexaenoic acid (DHA; 22:6n-3) have been shown in the brains of Alzheimer's patients (AD) as compared with normal age-matched individuals. Furthermore, low serum DHA is a significant risk factor for the development of AD. The relative concentration of DHA and other fatty acids, however, in the plasma of AD patients compared with patients with other kinds of dementias (other dementias; OD), patients who are cognitively impaired but nondemented (CIND), or normal patients is not known. In this study we analyzed the total phospholipid, phosphatidylcholine (PC), phosphatidylethanolamine (PE), and lysophosphatidylcholine (lysoPC) fractions of plasma from patients diagnosed with AD, OD, or CIND and compared them with a group of elderly control subjects with normal cognitive functioning. Plasma phospholipid and PC levels of 20:5n-3, DHA, total n-3 fatty acids, and the n-3/n-6 ratio were lower in the AD, OD, and CIND groups. Plasma phospholipid 24:0 was lower in the AD, OD, and CIND groups as compared with the group of control patients, and total n-6 fatty acid levels were higher in the AD and CIND groups only. In the plasma PE fraction, levels of 20:5n-3, DHA, and the total n-3 fatty acid levels were significantly lower in the AD, OD, and CIND groups. DHA levels were lower in the lysoPC fraction of CIND individuals only. There were no other differences in the fatty acid compositions of the different phospholipid fractions. Therefore, in AD, OD, and CIND individuals, low levels of n-3 fatty acids in the plasma may be a risk factor for cognitive impairment and/or dementia. Interestingly, a decreased level of plasma DHA was not limited to the AD patients but appears to be common in cognitive impairment with aging.

Huntington's disease has also been treated with fatty acids. A 6-month randomized, placebo-controlled pilot study of the E-EPA was carried out in seven (3 on EPA, 4 on PBO) in-patients with advanced (stage III) Huntington's disease. After 6 months, all the patients treated with E-EPA improved on the orofacial component of the Unified Huntington's Disease Rating Scale while all the patients on placebo deteriorated ( $p < 0.03$ ). Follow-up with 3D MRI brain scans with showed that while the placebo was associated with progressive cerebral atrophy, the E-EPA was associated with a reverse process ([Puri et al., 2002](#)).

## **Safety of PUFAs**

(Meydani, 1996) Cytokines are important biologic mediators with tightly regulated production. Overproduction contributes to pathogenesis of acute and chronic inflammatory, autoimmune, atherosclerotic, and neoplastic diseases. Animal and human studies have shown that production of cytokines can be reduced by long-chain (n-3) polyunsaturated fatty acids (PUFA). This, in turn, results in reduction of the severity of certain autoimmune, inflammatory, and atherosclerotic diseases and reduces cytokine-induced anorexia. Because these cytokines are also involved in control of the host defense, substantial reduction in their production could impair normal immune response. In addition, increased intake of (n-3) PUFAs without adequate antioxidant protection could result in increased free radical formation and lipid peroxidation, leading to a reduction in T cell-mediated function, natural killer cell activity, and macrophage cytotoxicity. These risks

associated with the intake of (n-3) PUFAs may be minimized without compromising its benefits by increasing intake of antioxidants such as vitamin E.

Experimental data support the notion that high intake of n-6 PUFAs may increase in vivo lipid peroxidation. This effect may be counteracted by dietary antioxidant supplementation. The influence of a high n-3 PUFA intake on measures of lipid peroxidation has been equivocal. In clinical trials, subjects who consumed diets rich in n-6 or n-3 PUFAs had fewer atherothrombotic endpoints than did control groups. A recent review discusses these issues and others including cholesterol and glucose metabolism, and hemostasis. Currently, daily intake of PUFAs as >10% of total energy is not recommended. Below this ceiling there is little evidence that high dietary intake of n-6 or n-3 PUFAs implies health risks ([Eritsland, 2000](#)).

### **Future Studies**

Additional studies with essential fatty acids are required for confirmation that dietary supplementation can affect the outcome of chronic and severe mental disorders. The National Institute of Mental Health has recently funded a larger study by Dr. Andrew Stoll at Harvard of fish oil supplementation in bipolar disorder, and the Stanley Foundation has recently initiated three separate clinical trials of fish oil in major depression, bipolar disorder, and schizophrenia.

The Stanley Foundation Bipolar Network (SFBN) was created to address the paucity of help studies in bipolar illness. The SFBN includes five core sites and a number of affiliated sites that have adopted consistent methodology for continuous longitudinal monitoring of patients. More than 500 patients are in continuous daily longitudinal follow-up. As of 2001, more than 93 had been randomized to n-3 fatty acids as an adjunct to mood stabilizers (Post et al., 2001).

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