Invited Review

Current Clinical Applications of Ω-6 and Ω-3 Fatty Acids

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ABSTRACT: *Background*: Recent years have brought a resurgence of research interest in fatty acids, with studied fields running the gamut of human disease. This movement has run in parallel with an increased interest in using nutrition modalities as therapeutic measures, as opposed to their conventional role as energy sources. The aim of this manuscript is to provide a basic review of current clinical applications of ω-6 and ω-3 fatty acids, with a particular focus on the latter. *Methods*: A selective review of the voluminous literature, including randomized controlled trials, meta-analyses, population studies, and case reports, was used to compile data and identify trends in pertinent clinical applications of fatty acid therapy. *Conclusions*: There are a myriad of disorders and maladies that seem to benefit from fatty acid supplementation, specifically ω-3 fatty acids. It has clearly been shown that ω-3 fatty acid supplementation provides a protective benefit in heart disease, and in particular sudden cardiac death. Rheumatoid arthritis (RA) is another disease entity that has been proven to benefit from this nutrition intervention, with improvement in symptoms and diminished nonsteroidal antiinflammatory drug (NSAID) usage. In addition, many psychiatric disorders, particularly schizophrenia and major depressive disorder (MDD), have shown positive results when supplementation has been used as an adjunct to standard pharmacotherapy. The remainder of clinical applications for ω-3 fatty acids requires further investigation. Specifically, according to preliminary clinical evidence, parenteral administration of fatty acids warrants further study.

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Essential fatty acids (EFA) are termed as such because they cannot be synthesized by the human body and thus must be derived from exogenous sources, namely, food. There are 2 EFA groups: ω-6
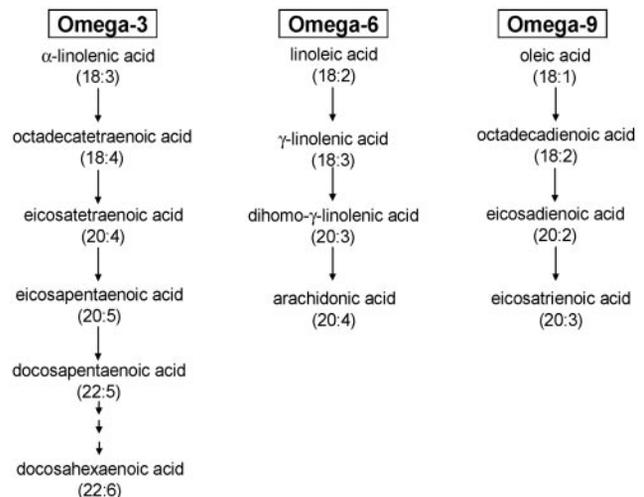

Figure 1. Fatty acid synthesis.

and ω-3. This nomenclature refers to the location of the double bond within the carbon backbone of the molecule. They are also characterized as polyunsaturated fatty acids (PUFA), which refers to the presence of 2 or more double bonds in their molecular structure.

Linoleic acid (LA) and α-linolenic acid (ALA) are essential PUFA of the ω-6 and ω-3 families, respectively (Figure 1). LA must first be converted to γ-linolenic acid (GLA) and then to arachidonic acid (AA), the biologically active compound. The downstream products of ALA are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). All of these fatty acids play an important role in cell membrane composition which, in turn, influences fluidity and cell surface biochemical signaling, and may serve as natural ligands for certain nuclear receptors that affect gene expression. In addition, AA and EPA are important eicosanoid and prostanoid precursors (Figure 2). AA products include 4-series leukotrienes and 2-series prostaglandins (prostaglandin E_2, prostacyclin I_2, thromboxane A_2), and these synthetic processes are mediated by 5-lipooxygenase and cyclooxygenase (COX) enzymes. EPA products include 5-series leukotrienes and 3-series prostaglandins (prostaglandin E_3, thromboxane A_3), and

Precursor of Eicosanoids

Figure 2. Ω-6 and ω-3 fatty acid metabolites.

Table 1
American Heart Association recommendations[13] for ω-3 fatty acid intake

All adults eat fish (particularly fatty fish) at least 2 times per week.
Patients with documented coronary heart disease should take 1 g of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) per day.
Patients with hypertriglyceridemia may benefit from EPA and DHA supplementation.

have dramatic effects on the development of certain human pathology. "Evolving" from hunter/gatherers to a "fast food nation" has not been without its untoward consequences.

Recent years have seen a resurgence of research interest in fatty acids, with studied fields running the gamut of human disease. This movement has run in parallel with an increased interest in using nutrition modalities as therapeutic measures (eg, dietary fiber, arginine, glutamine), as opposed to their standard nutrient-provider roles. The aim of this manuscript is to provide a basic review of current clinical applications of ω-6 and ω-3 fatty acids.

Cardiovascular Disease

Fatty acid supplementation in the treatment of cardiovascular and cerebrovascular diseases, such as coronary artery disease (CAD), arrhythmia, and cerebral vascular accident (CVA), has been well studied and documented over the past 20 years. Just recently, the findings of these clinical studies are making their way into the mainstream by way of official recommendations from the American Heart Association (AHA; Table 1).[13] Historically, the general and simplified view of ω-6 *vs* ω-3 fatty acids in a cardiovascular sense is that the former is proinflammatory and prothrombotic, whereas the latter is antiinflammatory and antithrombotic.[2,3] Following this line of reasoning, ω-6 fatty acids understandably have little to no role in the treatment of cardiovascular disease, except for their ability to lower serum cholesterol, whereas ω-3 fatty acids have been shown to be effective treatment in lowering serum triglycerides, CAD, arrhythmias, and CVA.

Earlier studies had differing results regarding the effect of ω-3 fatty acids on CAD. The US Health Professionals Study cited that increasing fish intake did not substantially reduce the risk of CAD among men who were initially disease-free.[14] CAD risk was stratified by end points, including fatal coronary disease (including sudden death), nonfatal myocardial infarction (MI), coronary artery bypass grafting, or angioplasty within the 6-year study. However, in the Western Electric Study, it was shown that there was an inverse association between fish consumption and CAD.[15] The major differences in this study

their synthesis is mediated by the same enzymes. EPA provides the substrate for a different array of lipid mediators, which are significantly less biologically active and, thus, less inflammatory than those derived from AA. More recently, it has been suggested that EPA, along with COX inhibition by aspirin, may result in the by-product production of resolvin E1, a possible endogenous antiinflammatory agent.[1] In simplified terms, AA products are thought to be proinflammatory mediators and EPA products are "anti-inflammatory," or rather less proinflammatory,[2–4] which makes their interaction critical, especially considering that AA and EPA are competitive substrates (Figure 2).[5] GLA further confuses the issue in that, when taken as a supplement, it is largely converted to dihomo-γ-linolenic acid (DGLA), which itself is also a competitor of AA,[6] rather than desaturated to AA. Also, GLA is a precursor of 1-series prostaglandins, which are less proinflammatory, similar to 3-series prostaglandins.

Ω-3 fatty acids are particularly rich in fish, marine animals such as seals, and nuts, whereas ω-6 fatty acids are concentrated in animal products and vegetable oils, which make up the majority of the modern Western diet. In an analysis of dietary changes spanning human evolution, Simopoulos comments that various factors, including industrialization and changes in human lifestyle, have led to a skewed ω-6 to ω-3 fatty acid ratio, approximately 16:1 in the current US diet as compared with 4:1 in Japan and 0.79:1 in the Paleolithic era.[7–11] When considering that diet is the significant determinant of cell membrane composition,[12] the presumed physiologic difference between these groups is likely to

were that the analyzed end point was CAD-associated mortality and the experimental time frame was 30 years. Specifically, increased fish consumption decreased death from MI by 42%. Interestingly, after subset analysis, it was shown that this inverse relationship was most significant in nonsudden death from MI, defined by the duration of the terminal illness and the place of death. Another major clinical study at the time, the Seattle Study, demonstrated the same inverse relationship between fish consumption and CAD but showed a marked decrease in sudden rather than nonsudden death.[16] Specifically, increased fish consumption decreased death from primary cardiac arrest by 50%.

Subsequent and contemporaneous studies were in accordance with the Seattle Study data as opposed to the Western Electric Study with regard to decrease in sudden *vs* nonsudden death.[17] However, there were some analyses that were directly opposed to the basic premise of the Seattle Study regarding decrease in primary cardiac arrest. The EURAMIC Study, a multicenter case-control study, showed no correlation between fish intake and the risk of primary MI in a cohort of men with no history of CAD or recent modification in dietary pattern.[18] In a slightly different study, the Diet and Reinfarction Trial (DART) examined all-cause mortality of men who were recovering from an MI, with variable dietary changes, in a randomized controlled manner.[19] It showed that dietary enrichment from fatty fish decreased mortality by 29% compared with ω-6 fatty acids and high-fiber diet. These disparate results most likely stem from the differences in study design and subject groups.

More recent studies have shown further support for the efficacy of fish oil supplementation as beneficial to patients with CAD. The official recommendations (Table 1) and scientific statement by the AHA were released in 2002 in favor of increased fish consumption and supplemental ω-3 fatty acids in people with documented coronary heart disease.[13,20] This comprehensive review by Kris-Etherton et al[13] cited epidemiologic population studies and randomized controlled studies, many of which have been discussed previously. Their thorough review also included *post hoc* analysis of studies such as the DART Study, which showed that the effect seen was secondary specifically to ω-3 fatty acids.[21]

Overall, clinical research is focusing more on direct supplementation with EPA, DHA, and ALA and their effects on secondary prevention, rather than simply fish ingestion.[22–24] The largest randomized controlled study to date with 11,000 patients, the GISSI-Prevenzione Study, showed a 15% reduction in cardiac mortality ($p < .02$), 20% reduction in all-cause mortality ($p = .01$), and 45% reduction in sudden-death mortality ($p < .001$).[22] The ω-3 fatty acid supplement given was a daily gelatin capsule containing 850–882 mg EPA and DHA in a ratio of 1:2, respectively. Although the evidence is increasingly in favor of a cardioprotection, it is not unani-

mous. Nilsen et al[25] showed that there was no relationship between ω-3 fatty acid ingestion and prevention of cardiac events in a population of Norwegian post-MI patients. Selected studies have also shown that ω-3 fatty acid supplementation improves cardiac status measured by angiography and the survival of vein grafts in coronary bypass graft patients,[26,27] but not restenosis rates in patients undergoing coronary angioplasty.[28,29] Further study, especially in the role of ALA, is warranted, although it is presently the consensus opinion that ω-3 fatty acids are beneficial in patients with CAD.[30]

Upon closer examination of the DART Study,[19] it was noted in a review by Leaf et al[31] that although there was a 29% decrease in mortality in the increased fish cohort, there was also an increase in MI. This suggests that there was another mechanism by which the cohort was improving mortality, namely, a reduction of arrhythmic deaths. Sudden cardiac death is death within 1 hour of symptoms, and the AHA defines it as a distinct entity from MI.[32] It is caused by sustained tachyarrhythmias, beginning as ventricular tachycardia and progressing to ventricular fibrillation. The major risk factor is coronary heart disease, as diseased myocytes are more prone to arrhythmia. The current hypothesis is that ω-3 fatty acids work by their direct effect on cell membrane composition and action potential propagation, as opposed to serving as a substrate for antiinflammatory and antithrombotic mediators.[31] *In vitro* and *in vivo* experiments have shown that ω-3 fatty acids have an electrically stabilizing effect on cell membranes *via* hyperpolarization.[33,34]

Reanalysis of the GISSI-Prevenzione Study showed that the reduction in all-cause mortality and cardiovascular mortality was mainly due to prevention of sudden cardiac death.[35] In addition, as previously mentioned, increased fish consumption has correlated with a nearly 50% reduction in sudden cardiac death.[17] There is an established body of evidence now indicating the beneficial effects of ω-3 fatty acids in preventing sudden cardiac death, likely through an antiarrhythmic mechanism.

The relationship between fish and ω-3 fatty acid intake on the incidence of CVA, or stroke, is not as well established as coronary disease and sudden cardiac death. Strokes can be ischemic or hemorrhagic. When coupled with the fact that ω-3 fatty acids are antithrombotic, the picture is certainly less straightforward than with coronary disease. In theory, they should be of benefit to ischemic events and harmful to hemorrhagic ones. What has been shown is that fish and fish oil consumption is indeed inversely related to the incidence of ischemic stroke and appears to have no effect on hemorrhagic stroke.[36–40] However, further and more rigorous study is warranted to verify these findings.

As mentioned before, there are limited therapeutic indications for ω-6 fatty acids in the setting of cardiovascular disease. Suggestions of clinical appli-

Table 2
Studies on cardiovascular disease

Study	Year	Fatty acid	Outcome
US Health Professionals[14]	1995	Increased fish intake	No relationship between fish intake and coronary artery disease (CAD) in initially disease-free patients.
Western Electric[15]	1997	Increased fish intake	Increased fish intake decreased death from myocardial infarction (MI) by 42%, most significantly nonsudden death.
Seattle[16]	1995	Increased fish intake	Increased fish intake decreased death from primary cardiac arrest, most significantly sudden death.
EURAMIC[18]	1999	Increased fish intake	No relationship between fish intake and risk of primary MI.
DART[19]	1989	Increased fish intake	Increased fish intake decreased mortality by 29% in patients recovering from MI, likely by reducing sudden death.
GISSI-Prevenzione[22]	1999	EPA, DHA	Ω-3 supplements reduced cardiac mortality by 15%, all-cause mortality by 20%, and sudden-death mortality by 45%.

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

cation have been confined to the specific ω-6 fatty acid GLA and to the realm of hypertension. Animal studies have shown that GLA, alone and in conjunction with EPA/DHA, induces an antihypertensive response.[41,42] Also, there is one clinical trial that showed that GLA and EPA supplementation resulted in decreased blood pressure in a cohort of patients with peripheral vascular disease.[43] Of course, the differential effects of this combination therapy are unknown.

Overall, there is a confirmed benefit to ω-3 fatty acid supplementation in the setting of cardiovascular disease, with much less evidence supporting ω-6 therapy (Table 2). The most significant ω-3 effect is the secondary prevention of sudden cardiac death due to arrhythmias. However, there are other far-reaching advantages in prevention of CAD and ischemic stroke, as well as some efficacy in treating hypertriglyceridemia and hypertension.[44,45] The AHA official recommendations reflect these thoughts (Table 1).[13] It is also important to note that the source of ω-3 fatty acids in therapy may significantly influence clinical efficacy. ALA, EPA, and DHA are all in the ω-3 fatty acid family but are also distinct compounds that differ in their abilities as therapeutic agents. Interconversion and its effects are also important considerations.

Pulmonary Disease

Lung disease has not demonstrated as much proven beneficial effect from fatty acid supplementation as its cardiovascular counterpart. However, the biologic theories upon which many studies have been founded are sound. The proposed impact of fatty acids on pulmonary disease is a direct result of their effects on the inflammatory cascade. As mentioned above, fatty acids are components of the cell membrane that serve as substrates for the synthesis of inflammatory mediators, such as prostaglandins, thromboxanes, and certain leukotrienes implicated in bronchoconstriction. The mediators are AA derivatives and end products of the ω-6 pathway. Hence, ω-3 fatty acids have been proposed as a treatment of pulmonary disease by a mechanism of down-regulating inflammatory mediators and up-regulating antiinflammatory substances (Figure 2). The areas of most intense research are asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF).

Asthma is a disease process characterized by almost continuous inflammation in the absence of significant triggers. Indeed, corticosteroids, potent anti-inflammatory agents, are a mainstay of therapy. Although it has been shown that neutrophil activity and leukotriene generation are decreased in patients treated with ω-3 fatty acids,[5] the clinical trial evidence has been underwhelming. In a review by Schwartz,[46] it was observed that there have been very few studies that have shown that ω-3 fatty acids are efficacious in asthma treatment. Dry and Vincent[47] showed that supplementing asthmatic patients with ω-3 fatty acids, in addition to inhaled steroids and nedocromil, for 9 months resulted in forced expiratory volume in 1 second (FEV_1) increase of 23%, compared with an increase of 10% in control groups treated with steroids and nedocromil alone. Surette et al,[48] in a randomized, double-blind, controlled trial treating patients with mild to moderate asthma, showed that combination therapy of ω-3 and ω-6 fatty acids (EPA and GLA) significantly reduced leukotriene synthesis and decreased inhaler dependence compared with placebo controls. The majority of adult studies, how-

ever, have shown no benefit to pulmonary function or clinical status.[46,49,50]

Several pediatric studies have been promising in the possible treatment and prevention of asthma. Hodge et al[51] showed that regular fish consumption (data ascertained by questionnaire) correlated with a decrease in wheezing and airway hyperresponsiveness, defined as >15% decrease in FEV_1 after exercise, in children. In a more tightly controlled study, using a cohort of hospital inpatient children to minimize environmental allergens and diet influence, Nagakura et al[52] showed that ω-3 fatty acid supplementation, given in a weight-based manner, resulted in an improvement of asthmatic symptoms and decrease in airway responsiveness to acetylcholine. The Childhood Asthma Prevention Study,[53] in progress now, published an 18-month update of their trial, monitoring the effects of fish oil administered from birth to a cohort preselected by asthma risk factors, with a planned endpoint of 5 years. They have so far noted a 10% reduction in prevalence of any wheezing and 8% reduction in prevalence of wheezing for longer than 1 week but no change in total asthma diagnoses. Overall, multiple reviewers have found that ω-3 fatty acids have not been proven to change clinical outcomes in asthma.[54]

COPD, specifically bronchitis, has been shown in epidemiologic studies to be decreased with increased ω-3 fatty acid intake. The National Health and Nutrition Examination Survey (NHANES) study showed a protective effect of fish consumption in chronic bronchitis.[55] Furthermore, Shahar et al[56] showed in a cross-sectional analysis that even smoking-related COPD, including bronchitis, emphysema, and spirometrically detected disease, were attenuated by ω-3 supplementation. Although these studies seem promising, the available literature is limited. The majority of COPD-focused studies concentrate on asthma, as detailed above.

CF is an autosomal recessive disease characterized by defective chloride transport. It is manifested by thick mucus secretions, primarily in the lung and pancreas. Regarding possible significance of fatty acid therapy, analysis of erythrocyte membranes in CF patients shows low levels of LA and EPA,[57] and the chronic inflammation present is leukotriene-mediated. Hence, ω-3 fatty acids have been promoted as a possible treatment modality *via* its correction of fatty acid composition abnormalities and its antiinflammatory effects. Isolated studies have shown a decrease in inflammatory mediators with ω-3 supplementation, which correlate with a change in fatty acid membrane composition,[58] but evidence for clinically significant alterations, such as improved FEV_1 or decreased sputum production, is lacking. In fact, 2 reviews within the last 5 years have noted that although some beneficial effects have been noted, there has yet to be a comprehensive study regarding the utility of ω-3 fatty acids in this disease entity.[59,60]

Overall, PUFA as a treatment modality for pulmonary disease is not proven to change clinical outcomes. However, supplementation does change biochemical profiles. Therefore, it is possible that past studies have been using subtherapeutic dosages, inadequate length of treatment time, or lack of controls for confounding variables such as environmental allergens and disparity of diet. Clearly, there is a need for a large, multicenter, randomized, controlled study to examine the effects of fatty acid supplementation in pulmonary disease, especially in light of the largely positive findings in the cardiovascular literature.

Gastrointestinal Disease

The most thoroughly studied gastrointestinal disease process has been inflammatory bowel disease (IBD). Fatty acid therapy has been proposed in both ulcerative colitis (UC) and Crohn's disease. The mechanism of action in these diseases of chronic inflammation is ω-3 fatty acid immunomodulation *via* down-regulation of proinflammatory cytokines. In addition, there may be a use for ω-6 fatty acids as well in providing supplementation for potentially EFA-deficient patients.[61]

In a comprehensive review of the literature, MacLean et al[62] discovered that there is a relative dearth of well-executed studies and no consensus of significant findings. They found that the majority of studies were underpowered and had insufficient data to assess outcomes. Specifically, they examined appropriate studies for the following end points: clinical score, endoscopic score, histologic score, relapse, remission, and corticosteroid requirement.

More analysis is required to learn whether there is a true role for fatty acid therapy in IBD. One promising study examined the efficacy of enteric-coated fish oil on Crohn's disease relapse.[63] Enteric-coated preparations deliver fatty acids in one-third the dose previously studied and also decrease unpleasant side effects, such as bad taste, flatulence, heartburn, halitosis, belching, and diarrhea. Using this mode of delivery, fish oil was administered to Crohn's patients in remission, and rates of relapse were measured. Relapse was defined as an increase in Crohn's disease activity index (CDAI) to 100 points above baseline or a score above 150 for >2 weeks. The enteric-coated fish oil cohort had a 28% rate of relapse compared with 69% in the placebo group ($p < .001$). In addition, following groups out to 1 year, the fish oil group maintained 59% remission, whereas the placebo group could manage only 26% ($p = .003$). This study's unique mode of delivery made it notable, especially when compared with other trials that saw no significant change in relapse rates.[64,65]

A recent randomized, controlled trial, which was not included in the MacLean et al[62] review, has come from the Cleveland Clinic and describes a beneficial effect of a fish oil supplement on cortico-

Table 3
Studies on autoimmune disease

Study	Year	Fatty acid	Outcome
Wakai et al[70]	2001	GLA	Clinical improvement of seasonal allergic rhinoconjunctivitis.
Hoff et al[71]	2005	EPA (membrane levels)	High membrane levels of EPA associated with decreased allergic rhinitis.
James and Cleland[73]	1997	—	Literature review confirms that double-blind, placebo-controlled trials show that fish oil supplementation improves symptoms of rheumatoid arthritis.
Kremer et al[74]	1995	Fish oil	Double-blind, placebo-controlled study shows fish oil supplementation improves symptoms of rheumatoid arthritis.
Zurier et al[77]	1996	GLA	Significant reduction in signs and symptoms of rheumatoid arthritis activity with GLA supplementation.
Mayser et al[78]	2002	Ω-3 fatty acid, parenteral	Clinical parameters of psoriasis were decreased in large percentage of treatment group compared to placebo.
Mayser et al[79]	2002	Ω-3 and ω-6 fatty acid, parenteral	Improvement in atopic dermatitis symptoms in IV ω-3 and ω-6 groups, with a decreased disease severity score in the ω-3 group.
Callaway et al[80]	2005	Hempseed oil (ω-3 and ω-6 fatty acids)	Improvement in itchiness and dryness associated with atopic dermatitis.
Bates et al[83]	1989	Ω-3 fatty acids	No significant difference in disability of relapse rate of multiple sclerosis patients in treatment group *vs* placebo control.
Nordvik et al[84]	2000	Ω-3 fatty acids	Significant reduction in severity of multiple sclerosis as measured by Expanded Disability Status Scale.
Alexander et al[87]	2005	Arginine and canola oil (ω-3 and ω-6 fatty acids)	Reduced occurrence of negative post–renal transplant events, including organ rejection.
van der Heide et al[88]	1993	Fish oil	Improved renal function and decreased rejection in first-time transplant patients in treatment group compared to placebo control.

EPA, eicosapentaenoic acid; GLA, γ-linolenic acid.

steroid requirements in patients with active UC.[66] Notably, the supplement also contained fructo-oligosaccharides, gum arabic, vitamin E, vitamin C, and selenium. At 6 months, the supplemented cohort required significantly less prednisone to control clinical symptoms ($p < .001$), as measured by disease activity index (DAI). Lending more support to this finding is that, at baseline, the supplemented cohort had a worse DAI than the placebo group. The last study to show a possible beneficial effect on corticosteroid requirement in UC was from 1992,[65] further illustrating the paucity of literature regarding this subject.

Autoimmune Disease

This broad category of illnesses traverses normal system-oriented classifications to include entities such as rheumatoid arthritis (RA), psoriasis, atopic dermatitis, glomerulonephritis, multiple sclerosis (MS), and organ transplant rejection. The mechanism of attack is again *via* EPA substitution for AA at the substrate level to shunt COX and lipooxygenase toward antiinflammatory end products. In addition, there is evidence that ω-3 fatty acids downregulate interleukin-1 (IL-1) and tumor necrosis

factor-α (TNF-α), which, in turn, inhibits synthesis of acute phase proteins, T and B lymphocyte activation, and the febrile response.[67] In a pathophysiologic group with the common problem being an overactive systemic inflammatory response, ω-3 fatty acids and their broad antiinflammatory effects have obvious appeal (Table 3).

Theories suggest an overall EFA deficiency may predispose patients to allergic tendencies.[68] Individuals prone to allergies may have a higher EFA requirement and difficulty converting LA to GLA (ω-6). Supplementation of both GLA and EPA has been shown to decrease the number of natural killer cells in healthy individuals while having little effect on the levels of other immune cell types.[69] In a cross-sectional study, Wakai et al[70] showed clinical improvement of seasonal allergic rhinoconjunctivitis in patients receiving GLA supplements. Another study has shown that there is a statistically significant inverse association between allergic sensitization and the membrane content of the ω-3 fatty acid EPA.[71]

RA is one of the few areas of study that have shown proven clinical benefits from ω-3 fatty acid supplementation. Since 1985, numerous randomized, controlled trials have shown ω-3 fatty acid

supplementation or increase in fish consumption to improve clinical symptoms.[72–74] This was measured by various factors including decrease in nonsteroidal antiinflammatory drug (NSAID) requirement necessary to keep pain at baseline, decrease in morning stiffness, and decrease in number of painful joints. Interestingly, these effects did not take place until weeks after initiation of treatment and appeared to persist for weeks after termination of treatment, displaying a residual effect as membrane composition presumably reequilibrated.[75] Clinical research is now focusing on dose optimization, primary prevention in high-risk groups, and biochemical analysis of cytokine regulation (IL-1, TNF-α). There has also been some observed benefit of ω-6 fatty acid supplementation in the form of GLA, with findings similar to ω-3 therapy.[76,77]

There have been some implications for the use of fatty acids in the field of dermatology as well. Psoriasis and atopic dermatitis are both dermatologic disease processes that are mediated by an overly robust immune system. The former occurs by a mechanism of keratinocyte hyperproliferation and leukocyte infiltration, whereas the latter occurs by an overabundance of AA metabolites in the epidermis. Again, the therapeutic theory is that ω-3 fatty acid supplementation will decrease the ω-6 to ω-3 content ratio, thereby diminishing the substrate availability of proinflammatory AA and replacing its downstream products with EPA-derived metabolites. A recent European study in the psoriasis literature used a novel method of delivery not currently available in the US, namely, parenteral administration of an ω-3 fatty acid lipid emulsion.[78] This group had previously used dietary supplementation but moved to an IV model to ensure rapid availability and increased EPA levels in nonesterified form. They performed several studies, 2 of which were randomized, controlled designs, and showed as high as 76% responders in the ω-3 cohort compared with 25% in the ω-6 group within 10–14 days. The measured clinical parameters were erythema, lymphocyte infiltration, desquamation, and subjective scores. In addition, they showed that parenteral administration of ω-3 fatty acids resulted in a rapid increase of EPA metabolites within just 3 days.

This same group examined a 10-day course of parenteral fatty acids, both ω-3 and ω-6, in the setting of atopic dermatitis and found that patients had a significantly lower disease severity score in the ω-3 group but both groups were improved when compared with baseline ($p < .05$).[79] Interestingly, they also noted better long-term clinical outcomes in the ω-6 group. Another study looking at atopic dermatitis examined patients given a hempseed oil supplement, which contains both ω-3 and ω-6 fatty acids, over a 20-week period and saw a significant clinical improvement with respect to skin dryness/ itchiness and dermal medication use.[80] Both atopic dermatitis studies, however, showed no increase in serum AA. Analyzing the differential effect of ω-6 fatty acids, Van Gool et al,[81] in a randomized controlled trial, gave infants at high familial risk of atopic dermatitis either borage oil (100 mg GLA) or placebo for the first 6 months of life. Patients in the ω-6 group saw a decrease in the severity of disease but no effect on IgE levels. The possible benefit of either PUFA perhaps indicates that the mechanism in this disease entity is distinct from psoriasis.

Due to the variable nature of its targets, autoimmune diseases run the gamut of afflicted body systems. MS is a neurologic disease that results from inappropriate immunologic attack on myelin, with subsequent disruption of normal neuronal function. Dietary modifications already have a place here in prophylactic treatment, with the use of vitamin D and calcium to prevent the osteoporosis that is common in this disease. In the late 1980s, there were 2 studies that examined the effects of ω-3 fatty acid supplementation on disease treatment and progression. In a single-arm, open-label clinical trial, Cendrowski[82] showed a significant reduction in disease severity, as measured by Expanded Disability Status Scale (EDSS), and disease progression ($p < .05$), as measured by a disease progression index. In a more rigorous randomized, controlled trial, Bates et al[83] concluded that there was no significant difference in disability or relapse rates between treatment and placebo groups. In a more recent, but single-arm, open-label study, supplementation was shown to significantly reduce EDSS.[84] These disparate results were summarized in a recent review of the literature by Schwarz and Leweling,[85] who surmised that there is insufficient evidence demonstrating that a particular diet is beneficial in MS. Although epidemiologic studies suggest a positive relationship and several small studies suggest clinical improvement, larger controlled trials are required to make firm conclusions (Table 3).

The body system that actually spurred the interest of the immunomodulatory effects of PUFA was the sphere of renal illnesses. Glomerulonephritis was the first proposed disease entity that was hypothesized as being a positive responder. Currently, the renal literature regarding fatty acid supplementation focuses on IgA nephropathy and transplantation. The former is a process mediated by immune-complex deposition and the proposed mechanism of action by ω-3 fatty acids is interruption of the cytokine pathways. In a large, randomized clinical trial from the Mayo Clinic, it was shown that long-term supplementation (2 years) with a fish oil concentrate resulted in delayed clinical disease progression and that this effect persisted at >6 years' follow-up.[86]

Examining dietary prophylaxis in renal transplantation, Alexander et al[87] showed that a supplement including arginine and canola oil (ω-3 and ω-6) reduced occurrence of the following posttransplant (>30 days postoperative) complications: rejection episodes (5.4% *vs* 23.7%, $p = .01$), calcineurin inhib-

Table 4
Studies on oncology

Study	Year	Fatty Acid	Outcome
Terry et al[98]	2003	Increased fish intake, EPA, DHA	Indeterminate effect on hormone-dependent cancer.
Maillard et al[96]	2002	Measured fat composition	Ω-3 fatty acid percentage of total fat composition was inversely related to breast cancer risk.
EURAMIC[97]	1998	Measured fat composition	The ω-3 to ω-6 fatty acid ratio was inversely related to breast cancer risk.
Caygill et al[93]	1996	Measured fat intake	Increased fish oil consumption, when measured as percent of total fat intake, was inversely related to mortality caused by breast and colorectal cancer.
Anti et al[131]	1992	Fish oil supplementation	Reduced rectal mucosal proliferation in patients with adenomatous colonic polyps.
Bartram et al[132]	1993	Fish oil supplementation	No effect on rectal mucosal proliferation when the ω-3 to ω-6 fatty acid ratio was low.
Terry et al[106]	2004	-	Review of studies showed no relationship between marine fatty acid intake and prostate cancer risk.
Augustsson et al[95]	2003	Increased fish intake	Fish intake of >3 times per week was associated with a decreased prostate cancer risk and decreased risk of metastatic disease.

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

itor toxicity (9.2% *vs* 35.3%, p = .003), new-onset diabetes mellitus (2.3% *vs* 14.5%, p = .04), cardiac events (5% *vs* 17.1%, p = .05), and sepsis (6.5% *vs* 18.7%, p = .05). In another randomized, controlled study examining specifically fish oil, ω-3 fatty acid supplementation was examined in a cohort of first-time renal transplant patients treated with cyclosporine and prednisolone for immunosuppression.[88] Patients were treated with either fish oil or coconut oil during their first postoperative year. The fish oil group showed significantly improved glomerular filtration rate, effective renal plasma flow, and mean arterial pressure. Most importantly, they had significantly fewer rejection episodes, 20 in the control group *vs* 8 in the fish oil group (p = .029). They also tended toward improved 1-year graft survival, 97% *vs* 84%, although these results were not statistically significant. This field warrants further study but appears promising (Table 3).

Oncology

Several epidemiologic studies and meta-analyses examining the effects of dietary fat and cancer have been published, with conflicting results. Some studies showed a correlation between total fat intake and increased cancer risk.[89,90] Conversely, other studies failed to show this relationship.[91,92] Looking specifically at fish consumption, the same pattern holds true, with some studies demonstrating a protective effect against malignancy[93,94] and others that do not support this premise.[95–98] There is no consensus (Table 4). Although the epidemiologic data do not clearly define a role for ω-3 fatty acids, animal and experimental studies have shown suppression of tumor growth, particularly in breast, colon, and prostate cancer.[99–104]

There are several proposed theories on the mechanism of ω-3 fatty acids and tumor growth suppression. Studies suggest that ω-3 fatty acids may function by the following mechanisms: inhibiting synthesis of eicosanoids derived from AA, inhibiting cell mitosis, increasing apoptosis, inducing differentiation, inhibiting angiogenesis, or changing estrogen metabolism.[105–107] More than 1 mechanism may be involved in tumor suppression and some may dominate in certain tumor types (eg, alterations in estrogen metabolism may play a greater protective role in breast cancer[108]).

Proinflammatory eicosanoids derived from AA (prostaglandin E_2, leukotriene B_4, thromboxane A_2, 12-hydroxyeicosatetraenoic acid) have been shown to play a role in carcinogenesis.[107,109] In contrast, ω-3 fatty acids are the precursors for eicosanoids associated with antiinflammatory and possibly chemotherapeutic effects.[107] The competitive nature of these substrates provides a dual mechanism for possible therapy where ω-3 fatty acids both down-regulate ω-6 metabolites and up-regulate their own products. In addition, ω-3 fatty acids may decrease the production of estrogen by the same mechanism of competitive inhibition. The AA product, prostaglandin E_2, acts on P_{450} aromatase to increase the production of estrogen, and so any treatment that decreases AA metabolism would also result in a decrease in this hormone. This would be of obvious benefit in treating hormone-mediated tumors, such as estrogen-receptor-positive breast cancer.

Ω-6 and ω-3 fatty acids have been shown to have differential effects on cell division. Specifically, AA stimulates the secondary messenger protein kinase C, which is itself an important mitotic factor, and AA-metabolites have also been implicated in stimu-

lation of mitosis. Conversely, ω-3 fatty acids have a stimulatory effect on programmed cell death, or apoptosis, by down-regulating nuclear factor κB (NFκB) and Bcl-2, mechanisms that are both over-expressed in cancer cells.[105] In addition, terminally differentiated cells do not multiply and ω-3 fatty acids have been demonstrated to induce differentiation of breast cancer cells.[110] Finally, ω-3 fatty acids are thought to contribute to angiogenesis inhibition by suppressing ω-6 products.[111–114]

Regarding chemotherapy, EFA supplementation, both ω-3 and ω-6, may enhance the effects of several agents, including doxorubicin, cisplatin, carboplatin, idarubicin, mitoxantrone, paclitaxel, tamoxifen, vincristine, and vinblastine, although these studies are at the preliminary *in vitro* stage.[115–120]

Breast cancer is the most common malignancy among women in the US, making up 32% of all cases,[121] and the second most common cause of cancer-related death in this group. Epidemiologic studies have not been able to demonstrate a correlation with total dietary fat intake and breast cancer risk.[91,92,122,123] Looking more specifically at fish oil, there is no consistent evidence of any protective effect.[98] However, it is possible that the ω-3:ω-6 ratio may have an effect on the cancer progression. In a multicenter study, total ω-3 and ω-6 fatty acid levels in adipose tissue demonstrated no correlation with breast cancer risk.[97] However, the ω-3:ω-6 ratio had an inverse relationship with risk in 4 of 5 centers. In addition, women in the highest tertile of ω-3:ω-6 ratio had a 30% lower breast cancer risk than women in the lowest tertile. This hypothesis was supported in a study by Maillard et al,[96] who also found an inverse ratio to risk association.

Although ω-3 fatty acids have been shown to inhibit the proliferation of breast cancer cells *in vitro* and in animal models,[98] clinical studies are lacking. Murine models have demonstrated that high ω-3 fatty acid intake inhibits human breast cancer growth and metastases.[101,124,125] There are some clinical studies that suggest improved response to chemotherapeutic agents in those patients with higher ω-3 fatty acid levels, but there are no published studies examining the direct effects of supplementation in breast cancer reduction.[126,127] One clinical trial is currently under way by the National Cancer Institute studying the effects of ω-3 fatty acids in breast cancer prevention in high-risk women.

Colon cancer is the third most common cancer for men and women in the US and the second most common cause of cancer-related death.[121] Migration studies suggest that environmental factors, including fat consumption, may have an effect on the development of colon cancer. However, it is now recognized that the pattern of fat consumption, rather than total fat consumption, may have more bearing on occurrence. One population study reviewed mortality data from 24 European countries and found an inverse relationship between ω-3:ω-6

ratio and colorectal cancer in countries with high-animal-fat diets. This study supports the hypothesis that consuming diets high in fat from fish, as opposed to diets high in fat from red meat, could reduce risk.[93] *In vitro* and animal studies have also demonstrated a possible protective role of fish oil and ω-3 fatty acids.[104,128–130] In a murine model, Deschner et al[100] showed that epithelial cell proliferation secondary to azoxymethane was greater in low ω-3:ω-6 ratio diets and, conversely, that a high-ratio diet resulted in less dysplasia.

The effects of ω-3 fatty acids on rectal cell proliferation in healthy patients and in patients at risk for colon cancer have also been studied. In the first published study by Anti et al,[131] patients with sporadic adenomatous colorectal polyps were given ω-3 fatty acids and had a greater reduction in rectal mucosal cell proliferation than placebo-treated patients. In a 1994 follow-up study attempting to find an optimal dose for fish oil supplementation, they found decreased rectal mucosal AA levels and increased levels of mucosal EPA and DHA in patients with sporadic colonic adenomas taking doses as low as 2.5 g/day of fish oil.[131] Of note, these data were only significant in patients with abnormal proliferation upon entry into the study. Although this trial examined the effects of fish oil in patients at increased risk for developing colon cancer, Bartram et al[132] examined these effects in healthy subjects and found that although rectal mucosal cell proliferation was decreased in patients taking fish oil, levels of mucosal membrane fatty acids were not actually increased. In their follow-up study, they again found no effect on mucosal fatty acid composition and, in addition, no effect of ω-3 consumption on rectal mucosal cell proliferation when the ratio of ω-3:ω-6 was low. Although there seems to be a protective effect of a higher ω-3:ω-6 ratio, the mechanism of action has yet to be defined.

Prostate cancer is the most common malignancy among men in the US and the second most common cause of cancer death.[121] Experimental and animal models seem to support the protective effect of ω-3 fatty acids on prostate cancer.[133,134] Animal studies by Rose and Connolly[135] showed EPA/DHA-induced growth inhibition of human prostate cancer cell lines in mice.[136] Another study performed in mice injected with human prostate cancer cells showed a decreased tumor weight in animals receiving ω-3 (menhaden oil) diets compared with those receiving the ω-6 diets.[136]

The role of dietary fat and prostate cancer in human populations has been extensively reviewed, and yet no clear association has been established. A review of the epidemiologic literature by Terry et al[106] did not find a clear association of marine fatty acids and prostate cancer risk. Study variability regarding classification of fish consumed, direct measurement of marine fatty acid, and tissue concentration of marine fatty acid content have made it difficult to draw consistent conclusions. Other recent

studies have even shown a possible increased risk association with ALA as opposed to the longer chain ω-3 fatty acids (EPA and DHA).[137,138] There is some support in the literature suggesting a stronger role of marine fatty acids in metastatic prostate cancer.[95,139] In a recent follow-up study by Augustsson et al,[95] eating fish >3 times per week reduced the risk of prostate cancer, particularly in patients with metastatic cancer, where risk was decreased by 24%. An appropriate prospective clinical trial is needed to properly elucidate the role of ω-3 fatty acids in this disease.

Psychiatry

There is substantial evidence that low levels of essential PUFA may play a role in schizophrenia. Numerous studies have demonstrated not only decreased levels of DHA and AA in schizophrenic patients but also evidence of aberrant fatty acid metabolism associated with this disorder.[140–150] Research indicating that schizophrenics exhibit lower PUFA than controls, taken with the fact that the brain is largely composed of PUFA (particularly AA and DHA) and that altered lipid profiles affect neurotransmission and behavior, give a foundation for using supplementation as a treatment modality.[142,148,151] In the epidemiologic literature, a 2-year study found that diets high in PUFA are correlated with a favorable outcome for schizophrenics.[152] Other studies further support this relationship between PUFA and symptom severity.[153,154]

The rationale for using PUFA in the treatment of schizophrenia is rooted in the observation that irregularities exist in the membrane phospholipid composition of both erythrocytes and postmortem brain tissue of schizophrenic patients.[141,143,145,149,150,155] Many studies have included drug-naïve, first-episode patients in their analyses and have reported that these patients also exhibit low levels of PUFA compared with control, suggesting that this trait is present at the time of disease onset and is not a product of treatment.[140,144,146] Schizophrenic patients have also been shown to exhibit an abnormal response to the niacin skin flush test, which elicits flushing of the face and neck in normal subjects and is the result of prostaglandin-induced vasodilation. A number of studies found that schizophrenics are significantly less likely to exhibit a positive niacin test, though this finding was not universal.[156–160] This lack of response indicates abnormal prostaglandin signaling in schizophrenics and adheres to the abnormal PUFA profile hypothesis in that prostaglandin D_2, which is directly involved in the niacin test, is synthesized from AA.

Numerous clinical studies have been conducted in which either ω-3 or ω-6 fatty acids are given in combination with standard therapy. Many studies have shown symptomatic improvement with supplementation of ω-3 fatty acids, particularly EPA. One case was reported in which a patient was treated solely with EPA and showed a marked reduction in both positive and negative symptoms.[161] In one study, Peet et al[162] administered 2 g/day EPA, 2 g/day DHA, or placebo to 45 symptomatic patients as an adjunct to antipsychotics over 3 months. According to assessment using the Positive and Negative Syndrome Scale (PANSS), patients who received EPA had significantly greater improvement of their positive symptoms than those receiving DHA or placebo. In a second study by the same group, EPA was used as the sole treatment, rather than as an add-on to antipsychotic medication. Patients were divided into 2 groups receiving either EPA or placebo and were given conventional antipsychotic drugs when it was considered clinically imperative. At the conclusion of the 3-month study, all 12 patients in the placebo group, but only 8 of 14 patients receiving EPA, were being treated with antipsychotics. It is noteworthy that patients being treated with EPA showed decreased PANSS scores, indicating that, although it might be better than no treatment, EPA may not be clinically effective as monotherapy.

Another trial administered various doses of EPA to 115 medicated schizophrenic patients for 12 weeks and measured changes in PANSS scores.[163] Patients receiving the antipsychotic clozapine in combination with EPA showed significantly greater improvement than that of the placebo group, the effect being greatest at 2 g/day. A similar study conducted by Emsley et al[164] found a significantly greater reduction of PANSS scores, as well as dyskinesia scores, in the EPA group than in the placebo group. Subsequent studies of the effects of PUFA on tardive dyskinesia have been varied.[147] Conversely, another trial was done in which no differences were found between patients receiving EPA and placebo, as measured by a battery of clinical rating scores, including PANSS.[165] However, it was pointed out in a letter to the editor by Horrobin[166] that these results could be attributed to improper dosing and duration of treatment, or to the fact that these patients were severe cases and had been receiving antipsychotic drugs for a long period of time.

There has also been some research done on how ω-6 fatty acid supplementation affects schizophrenia.[154,167,168] Overall, these studies have been negative and have not shown the clinical promise that has been found in ω-3 fatty acid supplementation trials. Taken together, these studies suggest that supplementation with ω-3 fatty acids, particularly EPA, may be an effective add-on therapy to antipsychotic medication and, most importantly, that more research needs to be done to thoroughly understand the clinical potential of ω-3 fatty acid supplementation in the treatment of schizophrenia.

There is also a substantial body of evidence indicating that low levels of PUFA play a role in major depressive disorder (MDD). Many studies demonstrate an inverse relationship between MDD severity and ω-3 fatty acid levels.[169–172] It has also been

shown that the ratio of AA to EPA correlates with the severity of MDD as measured by the Hamilton Rating Scale, although it is unclear whether this altered PUFA ratio is a result of depression or whether it pre-dates the disorder.[169] The link between PUFA levels and postpartum depression has also been studied, and it has been shown that DHA content in mothers' milk, as well as their seafood consumption, predicts lower prevalence.[173]

Epidemiologic studies indicate a connection between oily fish consumption and a lower incidence of MDD and suicide attempt. Hibbeln[174] conducted an analysis of cross-national prevalence of depression and fish consumption and concluded that there is an inverse relationship between these 2 factors. A similar study conducted in Finland by Timonen et al[175] found that women who rarely eat fish have a 2.6-fold increase in their risk of developing depression compared with regular fish eaters. Interestingly, this effect was not observed for men that participated in this study. Various explanations for this gender effect are suggested, including differences in genetic input across sexes. In addition, animal studies suggest that women require fewer EFAs and that they retain them more effectively.[175–179] Another study conducted in Finland found a negative correlation between fish consumption and depressive symptoms as measured by the Beck Depression Inventory.[180] It should be noted that not all studies have demonstrated this effect. Other studies have been done using self-report questionnaires for depressed mood and dietary fatty acid consumption that do not report an association between depression and dietary fatty acid intake.[181,182]

A correlation has also been observed between low EPA levels and suicide attempt. A study done in China assessed erythrocyte EPA levels in 100 patients who had attempted suicide in comparison with control patients being treated for injuries associated with a car accident. Findings indicated that the group of patients that had attempted suicide had significantly lower erythrocyte EPA levels compared with the control group, lending further support to the relationship between ω-3 fatty acid levels and MDD.[183]

Although the findings have been varied, there is sufficient support for the role of low PUFA levels in depression to warrant clinical study. PUFA have been given either as monotherapy or adjunct therapy, and results have been varied. Nemets et al[184] assigned 20 patients with MDD to receive either placebo or ethyl-EPA (E-EPA) in addition to their current antidepressant therapy for 4 weeks. Patients receiving E-EPA showed significantly lower scores on the Hamilton Depression Rating Scale compared with the placebo group, indicating a highly significant benefit of ω-3 fatty acid supplementation in the treatment of MDD. Further support for the use of E-EPA in the treatment of depression can be derived from a study conducted by Peet et al[167] in which seventy patients were given

either placebo or E-EPA in a range of dosages in addition to their antidepressant therapy. A large difference in efficacy as measured by multiple rating scales of depression was observed between doses of E-EPA, and significant effects were seen in patients receiving as little as 1 g/day of E-EPA. In addition, an 8-week trial found that patients on ω-3 fatty acids had significantly reduced depressive symptoms.[185] There have also been clinical studies in which PUFA supplementation did not improve depression. Marangell et al[186] administered either placebo or DHA as monotherapy to patients for 6 weeks, rated their improvement on the Montgomery-Asberg Depression Rating Scale, and found no significant effect, suggesting that PUFA supplementation shows the most promise as an adjunct therapy. However, DHA might be expected to have different effects if EPA were the effective compound because there is little retroconversion of DHA to EPA.

Schizophrenia and MDD both have substantial evidence supporting the role of PUFA as effective therapeutic agents, especially when used in concert with traditional treatment. In addition to these, there are other psychiatric disorders for which PUFA supplementation may be an effective treatment methodology, such as bipolar disorder, borderline personality disorder, and attention deficit hyperactivity disorder, all of which have shown promising preliminary data.[187–193]

Critical Care

Traditionally, nutrition in critical care has been aimed toward fulfilling protein and energy requirements of the patient to support the systemic inflammatory response while maintaining metabolic homeostasis, particularly normoglycemia. However, it now has a more expanded role in providing actual immunomodulatory and therapeutic benefit. Many critically ill patients had systemic inflammatory response syndrome (SIRS), a state characterized by tachycardia, tachypnea, hypotension, hypoperfusion, oliguria, leukocytosis/leukopenia, and fever/hypothermia. It can result from a plethora of causes, such as trauma, perforated diverticulum, pneumonia, and injury but shares the common traits of hypoperfusion or an infectious or inflammatory focus. If left unchecked, SIRS can progress to sepsis, severe sepsis, septic shock, multisystem organ failure, and death. Pertinent to our discussion is the fact that there are multiple cytokines that are upregulated in SIRS, the most significant of which are IL-1 and TNF-α. The hypothesis behind immunomodulatory nutrition is attenuation of this inflammatory cascade before end-organ damage occurs.

The majority of clinical studies have examined the effects of a combination of substances, including arginine, antioxidants, nucleotides, and the long-chain fatty acids that are salient to our discussion, delivered *via* the enteral route. A recent meta-

analysis of 22 randomized trials showed that immunonutrition significantly lowered infectious complications but not mortality.[194] However, there was marked heterogeneity across studies, and effects varied with type of intervention, patient population, and methodologic quality. Much of this may also be attributed to differing sources of ω-3 fatty acids, namely, ALA *vs* EPA/DHA supplementation, resulting in differential incorporation into cell membranes. Other reviews noted a reduction in number of ventilator days and length of hospital stay but again no change in mortality.[195,196] Analyzing mechanisms, *ex vivo* studies of serum from treated patients show a decrease in IL-6 and TNF-α compared with untreated controls.[197] Clear benefit for immunonutrition appears to be found in patients after major abdominal surgery but less clear evidence for improved outcome in other forms of critical illness. In part, this may be due to differing amounts of arginine used as well as to differing sources of ω-3 fatty acids from either EPA or ALA sources.

Acute respiratory distress syndrome (ARDS), another critical care entity, results from pulmonary inflammation rather than systemic, as seen in SIRS. It is characterized by an inflammatory response, increased permeability (which causes fluid buildup), hypoxia, and pulmonary hypertension. In a multicenter, randomized, controlled trial, Gadek et al[198] fed critically ill patients with an enteral formula consisting of EPA (ω-3), GLA (ω-6), and antioxidants and showed that the treatment group had significant improvements in oxygenation, with lower ventilation variables, significantly fewer days of ventilatory support, and decreased length of stay in the intensive care unit (ICU). Analysis of bronchoalveolar lavage (BAL) fluid showed significantly fewer total cells and neutrophils in the treatment group. They also showed that only 8% of the treatment group developed new organ failure compared with 28% in the control group. BAL fluid was also studied by Pacht et al,[199] who showed that enteral supplementation of EPA, GLA, and antioxidants decreased the number of IL-8, leukotriene B$_4$, total neutrophils, and alveolar membrane permeability in the setting of ARDS.

In some cases, SIRS can progress to sepsis. Sepsis is SIRS plus an identifiable pathogen. Sepsis can further progress to severe sepsis, which is characterized by organ system failure, and septic shock, which is characterized by hypotension or use of vasopressor agents. In a large, multicenter trial, Galban et al[200] selected patients admitted to the ICU with Acute Physiology and Chronic Health Evaluation (APACHE) II scores of >10 and supplemented them enterally with Impact (Novartis, Minneapolis, MN), a tube feeding formula composed of arginine, nucleotides, and ω-3 fatty acids (3 g/L). They showed a significant reduction in mortality ($p < .05$), bacteremia ($p < .01$), and number of patients with >1 nosocomial infection ($p = .01$). They also noted that the mortality reduction was more pronounced in patients with less severe illness. To our knowledge, this is the only large-breadth study to show a mortality benefit, although there have been other large studies that have shown no mortality benefit. Kieft et al[201] showed no improvement in clinical outcomes (ICU length of stay, hospital length of stay, ventilator days, mortality, infectious complications) in a large study involving a heterogeneous ICU population. Indeed, some have shown that in the extremely ill (APACHE >20), immunonutrition may actually lead to an increase in mortality.[202] Whether or not these differential effects are due to ω-3 fatty acids, as opposed to arginine or some other component, has yet to be determined. It should also be noted that many of these studies differed in the source of ω-3 fatty acids in their immunonutrition. Considering that EPA is likely the most potent effector and that ALA conversion to EPA is approximately 10%, the bioavailability of EPA is significantly dependent on source. Standardization of this parameter across studies is necessary for accurate comparison of data.

It appears that there may be a benefit for infectious complications and possibly mortality as well, using enteral "combo" formulations, but it is impossible to attribute these effects to an individual component, let alone ω-3 or ω-6 fatty acids. In fact, it is also possible that these effects are the result of synergy rather than an individual factor. In a comprehensive review of the literature and postulating upon future considerations, Mayer et al[203] explored the possibility of parenteral supplementation with ω-3 fatty acids in the setting of sepsis. IV administration of lipids resulted in an immediate increase in plasma free fatty acids. In a pilot study, the same group compared ω-3 and ω-6 fatty acid parenteral supplementation in septic patients for 10 days.[204] They concluded that upon *ex vivo* stimulation, the ω-6 group had increased plasma-free fatty acid abnormality and impaired neutrophil function whereas the ω-3 group had increased 5-series leukotriene production (EPA-metabolites) and significantly improved neutrophil function. Studying clinical outcomes would be the next logical step. Of note, parenteral ω-3 fatty acid is not currently available in the US, although compassionate-use administration does occur.

Pediatrics

Long-chain EFAs have been implicated in the development of both term and preterm babies. The EFAs were previously not well supplemented in infant formulas, and clinical deficiency was suspected to arise in babies who were solely sustained on this nutrition. This manifested itself in the form of impaired growth, dermatologic abnormalities (dryness, desquamation, thickening), abnormal visual function, peripheral neuropathy, and neurodevelopment deficiencies.[205] Specifically, long-chain

Table 5
Comparison of parenteral fat emulsions (10 g fat/100 mL)

	Intralipid (Baxter Healthcare, Deerfield, IL; Fresenius Kabi, Bad Homburg, Germany)	Liposyn II (Hospira, Lake Forest, IL)	Omegaven (Fresenius AG, Bad Homburg, Germany)
Oil source (g)			
Soybean	10	5	0
Safflower	0	5	0
Fish	0	0	10
Fat composition (%)			
Linoleic	50	65	0.1–0.7
α-Linolenic	9	4	<0.2
Eicosapentaenoic	0	0	1.28–2.82
Docosahexaenoic	0	0	1.44–3.09
Oleic	26	17.7	0.6–1.3
Palmitic	10	8.8	0.25–1
Stearic	3.5	3.4	0.05–0.2

fatty acids and their effect on cell membrane composition, and subsequently membrane fluidity, are thought to be vital in the development and function of neural tissue, which typically have membranes rich in these components. The rod photoreceptor in the retina has membranes composed of 30%–40% DHA.[206] Current research focuses on which particular fatty acids are required, LA and ALA as opposed to downstream products like EPA, DHA, and AA, and in what proportions for proper development.

In a comprehensive review, Fleith and Clandinin[207] concluded that ω-3 fatty acid supplementation resulted in an overall benefit to visual acuity and cognitive development in both term and preterm infants. Deficiency has been shown to be largely responsible for deficits in visual acuity and neurodevelopment, and supplementation with DHA and AA returns both term and preterm infants to the gold standard baseline of breast feeding,[208,209] with vision being measured by sweep visual evoked potential (VEP) acuity and forced-choice preferential-looking acuity. However, the reviewers also noted that fewer than half of all studies have found beneficial effects, indicating that the data are far from overwhelming. Indeed, in 2 sequential reviews for the Cochrane Database, Simmer[210] reported that there is no proven benefit in either term or preterm babies for fatty acid supplementation.[211] Ten and 11 studies were examined of term and preterm infants, respectively, all of which were randomized trials with clinical end-points. The disparity of data can be attributed in part to the varied methods of lipid administration (different lipids in varying dosages), different methods of visual and cognitive development (VEP, Teller acuity cards, electroretinography, IQ tests, Bayley Scales of Infant Development, Fagan infant test, language development), and different timed end points ranging from 4 weeks to 3 years. For these reasons, it is difficult to establish consistency in the data.

Novel Uses

Parenteral nutrition (PN) is an invaluable mode of "feeding" patients who are unable to absorb nutrients enterally.[212] PN is composed of a carbohydrate, protein, and lipid component. The lipid supplement is used to provide a high-calorie nutrient and to prevent EFA deficiency. The standard lipid used is a soy-based product that is primarily ω-6 fatty acids (Table 5). PN-dependent patients can be further subdivided into short- and long-term groups. The former usually includes surgical patients who had obstruction or prolonged ileus and ICU patients. The latter includes patients who had short bowel syndrome secondary to massive bowel resection, usually secondary to midgut volvulus or necrotizing enterocolitis (NEC). More than 30,000 patients in this country are wholly dependent on receiving PN.[213] One of the major complications of long-term PN is cholestasis and liver injury, also called PN-associated liver disease (PNALD). This iatrogenic entity is especially pronounced and deadly in infants with short bowel syndrome who have only long-term PN as their source of nutrition. The etiology of PNALD is unknown, but it has been suggested that the fat emulsion may play a key role in causing cholestasis and steatosis.[214,215]

Our group at Children's Hospital Boston has proposed that substituting an ω-3 lipid emulsion for the standard ω-6 formulation may alleviate cholestasis and stem the tide of PNALD (Table 5). In a short series, we have found that infants with PNALD treated with parenteral ω-3 fatty acids experience complete normalization of direct bilirubin (DB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and C-reactive protein (CRP), despite continued dependence receiving PN. This intervention was also sufficient to prevent EFA deficiency. Historically, these patients would only be expected to improve with resumption of enteral feeds and termination of PN.[216] A full, randomized, controlled trial is in preparation. As noted above, the use of parenteral ω-3 fatty acids is not

available in this country, and all uses described here were conditionally approved for compassionate use.

Conclusion

There are a myriad of disorders and maladies that seem to benefit from fatty acid supplementation, specifically, ω-3 fatty acids. However, the actual proven interventions, which have withstood vigorous analysis, are less than might be imagined. It has clearly been shown that ω-3 fatty acid supplementation provides a protective benefit in heart disease, and in particular, sudden cardiac death. This has been reflected in the AHA's official recommendations regarding the subject (Table 1). RA is another disease entity that has been proven to benefit from this nutrition intervention, with improvement in symptoms and diminished NSAID usage. In addition, many psychiatric disorders, particularly schizophrenia and MDD, have shown positive results when supplementation has been used as an adjunct to standard pharmacotherapy.

The remainder of clinical applications for ω-3 fatty acids requires further investigation. There are suggestions of benefit, but there are too many discrepancies in study design and too much variability in the data. In some cases, there is biochemical evidence of effect but no concurrent clinical improvement, indicating that treatment regimens with respect to length and dosages need to be optimized. There is undoubtedly a sound scientific basis for these hypotheses and so further study is certainly warranted. Indeed, perhaps the reason why there are such "across-the-board" effects of ω-3 fatty acids is because we are returning the body to its physiologic baseline, or the "way we were supposed to be." It is no coincidence that the ω-6 to ω-3 ratio disparity between the modern western diet (17:1)[217] and the Inuit diet of the Eskimos in Greenland (1:1) was accompanied by such an epidemiologic disparity in disease incidence with, for example, 45% and 7% mortality due to cardiovascular disease, respectively.[218]

Clinical applications are also beginning to examine the possible benefits to direct parenteral administration of fatty acids. Typically, enteral supplementation requires at least a few weeks and sometimes up to months for therapeutic benefit to be realized; conversely, the beneficial effects can linger for months after discontinuation of treatment. Direct IV supplementation could exponentially hasten these benefits, by perhaps bypassing the "first-pass" effect of the enterohepatic circuit, directly increasing plasma free fatty acid levels or some other yet-to-be-discovered mechanism. It is only now being rigorously investigated in the critical care and pediatric surgery fields.

One of the truly remarkable aspects of ω-3 fatty acids is that there have been virtually no deleterious side effects reported. Biochemically, it may have been expected that excessive supplementation would lead to bleeding complications due to its antithrombotic effects, but this has never been reported in the literature. It is unknown if supplementation might have clinically significant side effects in high-risk populations, such as patients who are chronically anticoagulated or with coagulopathies. Some enteral capsule formulations have been noted to have unpleasant side effects of diarrhea, flatulence, and "fishy burps," but certainly nothing critical. From a cost-benefit perspective, oral preparations of ω-3 fatty acids are patently available without a prescription and at reasonable prices at the local drugstore. The cost of parenteral preparations is as yet unknown because this usage has not been approved thus far. Methyl mercury contamination of fish is another issue that has recently been raised regarding the safety of pregnant women and women of childbearing age. This typically affects larger fish, such as sharks and swordfish, which do not possess an especially high level of fat and certainly are not on par with the fish that are more often consumed, such as tuna and salmon. Regardless, it is important to know how much fish consumed, what type of fish, and from where the fish have been procured. The apparent benign nature of this treatment brings into question whether or not research is even necessary and perhaps we should supplement indiscriminately. Although it is the authors' opinion that research should not only continue but efforts should be doubled, it would not be unreasonable for some movement on the part of the agricultural and food industries to move the Western diet toward a healthier ω-6 to ω-3 ratio, considering its apparent widespread benefits and dearth of side effects.

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