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Parenteral nutrition with *n*-3 lipids in sepsis

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Dietary supplements of *n*-3 fatty acids have long been used to influence chronic inflammatory disorders. Recent studies with an immune-enhancing diet partly based on *n*-3 fatty acids report beneficial effects in patients with acute hyper-inflammatory diseases, such as the sepsis syndrome or adult respiratory distress syndrome (ARDS). The possible suppression of exaggerated leucocyte activity, the improvement of microcirculatory events, as well as the opportunity to administer intravenous lipids enriched in *n*-3 fatty acids signal the possibility of a combination of parenteral caloric support and pharmacological intervention. Using parenteral administration of fish oil-based lipids, a new rapid and highly effective anti-inflammatory agent may allow the option to alter the immune status in hyper-inflammatory diseases such as sepsis and ARDS.

***n*-3 Fatty acids: Fish oil: Parenteral nutrition: Sepsis: Cytokines: Inflammation**

Introduction

Recent advances have shown that supply of selective additives to nutritional regimens can influence inflammatory and immunological processes of diseases. *n*-3 Lipids are capable of modulating lipid-mediator synthesis, cytokine release, leucocyte activity, and endothelial cell activation. This review deals with the molecular mechanisms and cellular functions in hyper-inflammatory diseases, such as sepsis and adult respiratory distress syndrome (ARDS). It emphasizes the potential benefit of *n*-3 lipids in enteral and parenteral nutrition, heralding the possibility to combine nutrition and pharmacological intervention. The dilemma of adequate timing of anti-inflammatory *n*-3 lipids in sepsis as a disease with alternating hyper- and hypoactive inflammatory phases will be discussed.

Pathophysiological aspects of sepsis

Sepsis and septic shock continue to be associated with high mortality rates ranging between 30 and 60 %, despite major advances in critical care medicine (Friedman *et al.* 1998; Wheeler & Bernard, 1999; Bone *et al.* 1997). Sepsis thus represents the major cause of death in critical care units worldwide. It is defined as the presence of two or more criteria of systemic inflammation: leukocytosis or leukopenia, tachycardia, tachypnea, and fever or hypothermia (Bone *et al.* 1992). With the onset of an organ system failure, sepsis is judged as severe, and hypotension or use of vasopressor agents signal the beginning of septic shock.

In healthy individuals a tightly regulated, potent and complex immunological cascade is responsible for the defense against invading organisms. Uncontrolled liberation of a multitude of pro-inflammatory and potentially autotoxic mediators has been described in experimental models of sepsis as well as under clinical conditions (Dinarello, 1997; Chabot *et al.* 1998; Heller *et al.* 1998). The fact that such a systemic inflammatory reaction may not only be triggered by microbial invasion, but is encountered in response to different kinds of tissue injury, is reflected by the term 'systemic inflammatory response syndrome' (SIRS). In addition to the causative organism, products released by bacteria such as endotoxins [lipopolysaccharide (LPS)], exotoxins, superantigens, or lipoteichoic acid may also trigger the excessive release of otherwise protective inflammatory mediators and lead to a hyper-inflammatory response harming the host (Fig. 1).

Polymorphonuclear granulocytes (PMN) are intimately involved in these events representing the first line of defense against microbial invasion but at the same time bearing the capacity to cause serious tissue destruction (Chabot *et al.* 1998; Yao *et al.* 1998). Monocytes are able to control the inflammatory cascades (Volk *et al.* 2000), based on their capacity to liberate both pro- and anti-inflammatory

Abbreviations: ARDS, adult respiratory distress syndrome; SIRS, systemic inflammatory response syndrome; CARS, compensatory anti-inflammatory response syndrome; FA, fatty acid; AA, arachidonic acid; Tx, thromboxane; LT, leukotriene; EPA, eicosapentaenoic acid; DAG, diacyglycerol.

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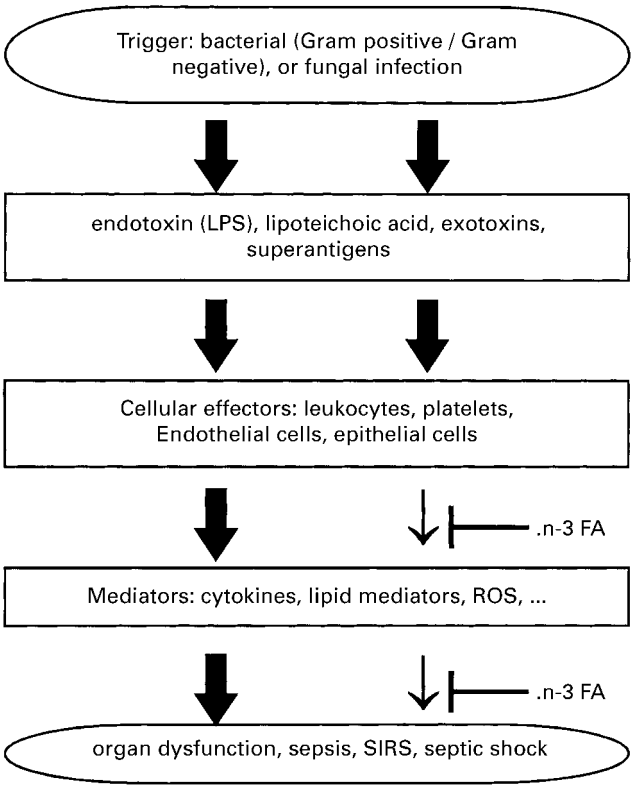

Fig. 1. Different levels of immunological control of inflammation and the postulated interaction of *n*-3 fatty acids. In sepsis uncontrolled and unrestricted upregulation of host defense takes place. *n*-3 Fatty acids interfere with the regulation and decrease the exaggerated response.

cytokines as well as chemokines regulating activation and recruitment of further leucocyte populations to the inflammatory focus.

In parallel to the inflammatory response to the inciting injury an anti-inflammatory reaction is initiated that has been coined 'compensatory anti-inflammatory response syndrome' (CARS) (Bone, 1996). It combines an upregulation of anti-inflammatory cytokines, impairment of neutrophil function and monocyte deactivation leading to an impaired host defense and enhanced susceptibility to secondary infections (Docke *et al.* 1997; Kox *et al.* 1997; Solomkin *et al.* 1984, 1981).

Biochemical basis of the anti-inflammatory effects of *n*-3 lipids: exogenous fatty acids influence inflammatory cell activation

Leucocytes, lipid mediators and cytokines: n-*3 fatty acids modulate the cellular response to an inflammatory trigger*

Lipid mediators are products derived from fatty acids (FA) such as arachidonic acid (AA) via lipoxygenase, cyclooxygenase and cytochrome P–450 pathways, and include eicosanoids [prostaglandins (PG), thromboxanes (Tx), leukotrienes (LT), lipoxins, hydroxy- and epoxy-fatty acids] and platelet-activating factor (PAF). Eicosanoids and PAF have long been implicated in both pro-inflammatory and anti-inflammatory events as occurring in sepsis (Heller *et al.* 1998; Mayer *et al.* 1998*b*). *In vitro*, inflammatory ligands are poor activators of neutrophil leukotriene synthesis. The latter characteristic changes fundamentally upon simultaneous addition of free precursor fatty acid; the application of exogenous AA amplifies LT generation (Grimminger *et al.* 1992). Bearing in mind that substantial levels of free AA are known to arise at sites of inflammatory events (Hammarström *et al.* 1975; Unterberg *et al.* 1987) this finding may be of major relevance.

The family of *n*-6 fatty acids including AA represents the predominant polyunsaturated fatty acids in common Western diets and current nutritional regimes. In contrast, *n*-3 fatty acids in which the last double bond is located between the third and fourth carbon atom from the methyl end, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), make up an appreciable part of the fat in cold-water fish and seal meat. They serve as alternative lipid precursors for both cyclooxygenase and lipoxygenase pathways, with the formation of trienoic prostanoids (instead of the 2-series originating from AA) and 5-series leukotrienes (LT) (instead of the 4-series LTs derived from AA) (Calder, 1998). EPA represents the preferred substrate for the lipoxygenase pathway compared to AA resulting in a higher formation of EPA-derived products at the expense of AA-derived metabolites when both free FA are simultaneously available. Many of the *n*-3 fatty acid-derived metabolites, including 5-series cysteinyl-LTs, LTB_5 and TxA_3, possess markedly reduced inflammatory and vasomotor potencies as compared to the AA-derived lipid mediators and may even exert antagonistic functions (Kragballe *et al.* 1987). Beyond their direct influence on the generation of eicosanoids, EPA and DHA modulate the inflammatory response by inhibiting the generation of pro-inflammatory cytokines: after several weeks of dietary *n*-3 fatty acids release of TNFα and IL-1 from mononuclear cells were suppressed (Endres *et al.* 1989; Caughey *et al.* 1996). Lymphocytes are extremely sensitive in their response to free polyunsaturated fatty acids (PUFA). Addition of free PUFA *in vitro* or dietary supplementation of PUFA were reported to suppress IL-2 production, antigen presentation, lymphocyte proliferation and natural killer cell activity (Calder, 1998).

Intracellular signal transduction – fatty acids modulate lipid signaling

In addition to the described consequences on inflammatory mediators, fatty acids influence the intracellular second messenger systems. Upon occupation of a receptor the phosphatidylinositol-specific phospholipase C (PI-PLC) is activated and cleaves PIP_2 to inositol-tris-phosphate (IP_3) and diacylglycerol (DAG). The produced amount of inositol-phosphates (IP_x) depends on the fatty acid composition of PIP_2. An increase in the content of *n*-3 PUFA in the PI pool leads to a reduced generation of IP_x and DAG and a subsequent decreased response of leucocytes to an inflammatory stimulus (Sperling *et al.* 1993). The DAG-dependent activation of the protein kinase C (PKC) is again influenced by the fatty acid composition of this second messenger, which is directly derived from the fatty acid composition of the lipid membrane. DAG with an *n*-3 fatty

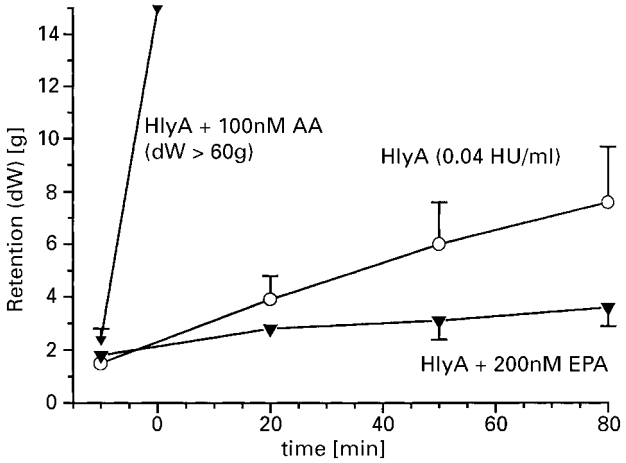

Fig. 2. Influence of free fatty acids in a model of septic lung failure. Acute septic lung failure was induced by injection of an exotoxin (*E. coli* hemolysin (HlyA)) into the pulmonary artery of an isolated rabbit lung. Simultaneous application of HlyA and free arachidonic acid (AA) aggravated the lung edema, in contrast, co-application of HlyA and free eicosapentaenoic acid (EPA) decreased the injury.

acid occupying the s*n*-2 position is less effective in activating PKC compared to DAG with an *n*-6 fatty acid. For complete activation of PKC the enzyme is translocated to the cell membrane binding to phosphatidylserine (PS). This process again is dependent on the FA composition of PS with *n*-3 FA decreasing the effectiveness of binding and activation (May *et al.* 1993; Terano *et al.* 1996). All these mechanisms may translate into a reduced inflammatory cell activation thereby increasing the anti-inflammatory effect of *n*-3 fatty acids.

Leucocytes, endothelial cells, and their interaction

The emigration of leucocytes from the intravascular compartment into the inflamed tissue is a fundamental process in many acute and chronic inflammatory diseases including ARDS and sepsis. It is required for both healing as well as perpetuating the chronic course. Leucocytes enter the tissue and leave the circulation by crossing the vascular endothelium. This process of transendothelial migration is a multistep mechanism, involving the tethering of leucocytes to the vessel wall, rolling on the endothelial cells, adhesion to the endothelium followed by movement of the leucocytes through the intercellular junctions into the inflamed tissue. Several adhesion molecules have been shown to be involved in the transendothelial migration, including β_2-integrins (CD11/CD18 complex), the β_1 integrins, selectins, ICAM-1 (intracellular adhesion molecule-1), PECAM-1 (platelet endothelial cell adhesion molecule-1) and VCAM-1 (vascular-cell adhesion molecule-1). Cytokines, such as TNF-α and IL-1 arising from the inflamed tissues facilitate the extravasation of leucocytes by increasing the expression of ICAM-1 and VCAM-1 on endothelial cells. (Spertini *et al.* 1992; Meerschaert & Furie, 1994; Muller *et al.* 1993; Andrew *et al.* 1998; Weber & Springer, 1998). *n*-3 Fatty acids are capable of reducing the TNF-induced expression of VCAM-1 on the endothelial surface. This leads to a reduced adhesion of leucocytes to endothelial cells and a subsequent transmigration into the inflamed tissue (DeCaterina *et al.* 1994; Weber *et al.* 1995) and may add to the anti-inflammatory effect of *n*-3 fatty acids.

Enteral nutrition versus parenteral lipid infusion

Effects of long-term dietary supplementation of volunteers or patients with *n*-3 are thoroughly described and result in suppression of experimentally induced immune responses such as the release of TNF-α by mononuclear leucocytes (Endres *et al.* 1989) or improve the course of hyper-inflammatory diseases (Calder, 1998; Mayer *et al.* 1998*b*). Weeks to months are needed for the full effect of *n*-3 fatty acids to become effective. In contrast, parenteral infusion of synthetic lipid aggregates activates endothelial lipoprotein lipases, including a translocation of the enzyme from the cellular binding site into the vascular compartment, with resultant immediate increase in plasma free fatty acids due to escape from local cellular uptake mechanisms (Peterson *et al.* 1990). Thus, parenteral infusion of lipids with *n*-3 fatty acids containing triglycerides overcomes kinetics and extent of dietary substitution by order of magnitude (Rustan *et al.* 1998; Lovegrove *et al.* 1997).

Sepsis and adult respiratory distress syndrome: experimental evidence and clinical outlook

Adult respiratory distress syndrome/acute lung injury– important lessons from experimental and clinical studies

ARDS, an acute inflammatory disorder of the lungs, was described as a syndrome of inflammation and increased permeability linked with radiological and physiological disturbances not caused by left atrial hypertension. New investigations promote the idea of a local imbalance of pro-inflammatory and anti-inflammatory cytokines as well as oxidative stress and antioxidants to increase the susceptibility to develop ARDS (Suter & Ricou, 1998; Quinlan *et al.* 1997). Moreover, TxA_2-mediated pulmonary hypertension and subsequent lung edema induced by leukotrienes, cytokines and other mediators are key features of this disease (Connelly & Repine, 1997). In models of acute lung injury the protective effect of *n*-3 fatty acids is well described. Acute intervention with infusion of either free AA or EPA aggravated or ameliorated respectively, pulmonary edema formation in a model of septic lung failure (Grimminger *et al.* 1997*b*, Fig. 2). Application of AA lead to exaggerated generation of leukotrienes and TxA_2 accompanied by circulatory disorders. In contrast, EPA induced the generation of 5-series leukotrienes, TxA_3 and reduced pulmonary hypertension (Grimminger *et al.* 1993; 1995; 1997*a*; 1997*b*; 2000). In line with this notion, dietary supplementation of *n*-3 fatty acids ameliorated experimental septic lung injury and exhibited organ-protective effects on the basis of similar changes: reduction of AA-derived pro-inflammatory metabolites, decrease in pulmonary hypertension, reduced pulmonary edema formation, and attenuated pulmonary neutrophil accumulation (Manusco *et al.* 1997*a*; 1997*b*; Murray *et al.* 1991; 1993; 1995; Sane *et al.* 2000). Based on these investigations, an important multi-center

study in patients with ARDS investigated the effect of enteral nutrition with EPA, γ-linoleic acid (GLA), and antioxidants on clinical outcome. The authors reported improved oxygenation, reduced days on ventilation, decreased incidence of new organ failure, and shortened length of stay in the intensive care unit (Gadek *et al.* 1999). However, the nutrition incorporated a mixture of EPA, GLA, and antioxidants and thus, no conclusion may be drawn whether only the combination or a single component was responsible for the therapeutic success. Moreover, no published clinical data are available concerning the effect of *parenteral n*-3 fatty acids on the course of ARDS. On the basis of the available experimental data and the study using dietary supplementation (Gadek *et al.* 1999) we speculate that parenteral nutrition using *n*-3 fatty acids will prove to be a useful tool for feeding patients with ARDS.

Sepsis and intravenous n-*3 fatty acids – when should intervention take place?*

As described above for the first phase of sepsis syndrome, supraphysiological levels of TNF-α and IL-1 appear to be key components, and are currently regarded as suitable targets for therapeutic intervention. Moreover, TNF-α- and IL-1-release by human monocytes can be effectively suppressed by dietary intake of *n*-3 lipids. We believe that this effect can be massively augmented in septic patients by using the parenteral route for lipid application, since intestinal losses due to lipid remodelling and incomplete absorption are bypassed. As already discussed, an extremely increased response to intravenous lipid infusion can be expected and increased levels of free fatty acids in septic patients without lipid infusion have already been detected (Bursten *et al.* 1996; Robin *et al.* 1981). This is probably due to different reasons. Plasma free fatty acid elevation is part of the general metabolic response syndrome to stress due to metabolic changes in liver and other organs (Weissman, 1990) and secretory phospholipase A_2 is elevated in sepsis (Guidet *et al.* 1996). Moreover, iatrogenic interventions as vasopressors, such as adrenaline or noradrenaline, preferentially increase the plasma levels of polyunsaturated free fatty acids by activating lipoprotein lipase and the hormone-sensitive triglyceride lipase of adipose tissue (Gavino & Gavino, 1992; Samra *et al.* 1996). Heparin, used in low doses in septic patients, is a well-known activator of the lipoprotein lipase (Jaume *et al.* 1996). Due to these reasons, a highly effective and rapid modulation of the inflammatory response can be expected.

However, conflicting results using *n*-3 lipids in different septic animal models have been published. Dietary *n*-3 lipid pre-treatment reduced survival in a murine model of intraperitoneal-induced systemic infection (Fritsche *et al.* 1997). Other authors have described increased circulating levels of TNF-α in mice pre-fed with fish oil and subsequently challenged with LPS (Blok *et al.* 1996). Chyi & Yeh have described no influence of dietary supplementation with lipids on the survival rate in a diabetic rat model of intraperitoneal sepsis accompanied by increased levels of inflammatory cytokines in the experimental group receiving dietary *n*-3 fatty acids (Chyi & Yeh, 2000). In a similar model using total parenteral nutrition, no differences in inflammatory cytokines were detected (Chao *et al.* 2000). On the other hand, beneficial effects of *n*-3 fatty acids on, for example, lung edema or splanchnic blood flow have been published (Sane *et al.* 2000; Pscheidl *et al.* 1994). These conflicting results may be due to the different conditions used: various species, different models (e.g. chronic intraperitoneal sepsis versus bolus LPS infusion), and dietary manipulations (enteral versus parenteral nutrition) result in diverging inflammatory consequences and outcome. A recent report affirms that the activation state alters the effect of *n*-3 fatty acids in murine macrophages (Mϕ): while fish oil decreases the inflammatory cytokine response in thioglycollate-elicited Mϕ it increases the production in resident Mϕ (Wallace *et al.* 2000).

Nutritional support in sepsis: alternating inflammatory status but rigid immunonutrition?

Considering sepsis in intensive care patients, it is essential to distinguish between early or acute sepsis syndrome with a hyperinflammatory cytokine profile and an exaggerated leucocyte response (i.e. SIRS), as well as chronic sepsis with immunoparalytic features (i.e. CARS). Against this background the application of any single anti-inflammatory or pro-inflammatory principle needs to be based on a careful and timely evaluation of the current immunological status of the individual patient. On one hand, excessive suppression of inflammatory leucocyte function will cause a decreased ability of the compromised host to fight against invading microorganisms and, on the other hand, an overamplified inflammatory response may harm the patient. However, there is a need for parenteral lipid nutrition in many septic patients, offering the future possibility of a combination of effective caloric support with immunomodulatory pharmacological therapy. The effect of oral versus intravenous lipid application may differ or may even be adverse, since intravenous infusion but not oral supplementation leads to a massive increase in plasma-free fatty acids (Mayer *et al.* 1998*a*).

In contrast to a parenteral lipid infusion based on *n*-3 fatty acids, an enteral diet supplemented with a combination of arginine, nucleotides, and fish oil was developed which incorporates different immune-modulatory agents. In the last few years, several studies using this enteral nutrition in septic patients have been published but to date only one study has demonstrated a significant positive impact on mortality. In a multicenter trial Bower *et al.* (1995) studied critically ill patients. They reported a reduced length of stay in hospital and decreased frequency of acquired infection, which was also true for the subgroup classified as septic. Using the same enteral nutrition in a single centre study, Atkinson *et al.* (1998) demonstrated that only patients with whom it was possible to achieve enteral nutrition displayed a significant benefit in terms of mechanical ventilation and length of stay in hospital. The most recent multicenter trial using the same enteral nutrition is the first to report a significant impact on mortality (Galban *et al.* 2000). The mortality was 17 from 89 in the study group and 28 from 87 in the control group ($P<0.05$). The study also reported a significant reduction in bacteremias and nosocomial

infections. In contrast to the other studies, no significant reduction in length of stay was stated. However, again it is unclear which of the additives resulted in the reported positive effects or whether only the combination of all was effective. Moreover, it is open to speculation whether a nutrition regime chosen to match the inflammatory demands of a single patient — either immune enhancing or anti-inflammatory — should incorporate all the components.

References

Andrew DP, Spellberg JP, Takimoto H, Schmits R, Mak TW & Zukowski MM (1998) Transendothelial migration and trafficking of leukocytes in LFA-1-deficient mice. *European Journal of Immunology* **28**, 1959–1969.

Atkinson S, Sieffert E, Bihari D & The Guy's Hospital Intensive Care Group (1998) A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill. *Critical Care Medicine* **26**, 1164–1172.

Blok WL, Debruijn MFTR, Leenen PJM, Eling WMC, Vanrooijen N, Stanley ER, Buurman WA & Vandermeer JWM (1996) Dietary *n*-3 fatty acids increase spleen size and postendotoxin circulating TNF in mice: role of macrophages, macrophage precursors, and colony stimulating factor 1. *Journal of Immunology* **157**, 5569–5573.

Bone RC (1996) Sepsis SIRS and CARS. *Critical Care Medicine* **24**, 1125–1128.

Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM & Sibbald WJ (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM consensus conference committee. American college of chest physicians/society of critical care medicine. *Chest* **101**, 1644–1655.

Bone RC, Grodzin CJ & Balk RA (1997) Sepsis: a new hypothesis for pathogenesis of the disease process. *Chest* **112**, 235–243.

Bower RH, Cerra FB, Bershadsky B, Licari JJ, Hoyt DB, Jensen GL, Van Buren CT, Rothkopf MM, Daly JM & Adelsberg BR (1995) Early enteral administration of a formula (Impact®) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. *Critical Care Medicine* **23**, 436–449.

Bursten SL, Federighi DA, Parsons P, Harris WE, Abraham E, Moore EE Jr., Moore FA, Bianco JA, Singer JW & Repine JE (1996) An increase in serum C18 unsaturated free fatty acids as a predictor of the development of acute respiratory distress syndrome. *Critical Care Medicine* **24**, 1129–1136.

Calder PC (1998) Immunoregulatory and anti-inflammatory effects of *n*-3 polyunsaturated fatty acids. *Brazilian Journal of Medical and Biological Research* **31**, 467–490.

Caughey GE, Mantzioris E, Gibson RA, Cleland LG & James MJ (1996) The effect on human tumor necrosis factor-α and interleukin 1β production of diets enriched in *n*-3 fatty acids from vegetable oil or fish oil. *American Journal of Clinical Nutrition* **63**, 116–122.

Chabot F, Mitchell JA, Gutteridge JM & Evans TW (1998) Reactive oxygen species in acute lung injury. *European Respiratory Journal* **11**, 745–757.

Chao CY, Yeh SL, Lin MT & Chen WJ (2000) Effects of parenteral infusion with fish-oil or safflower oil on hepatic lipids, plasma amino acids, and inflammatory mediators in septic rats. *Nutrition* **16**, 284–288.

Chyi A & Yeh S (2000) Effects of dietary fish oil on survival rate, plasma amino acid pattern, and inflammatory-related mediators in diabetic rats with sepsis. *Clinical Nutrition* **19**, 313–318.

Connelly KG & Repine JE (1997) Markers for predicting the development of acute respiratory distress syndrome. *Annual Review in Medicine* **48**, 429–445.

DeCaterina R, Cybulsky MI, Clinton SK, Gimbrone MA Jr. & Libby P (1994) The omega-3 fatty acid docosahexaenoate reduces cytokine-induced expression of proatherogenic and proinflammatory proteins in human endothelial cells. *Arteriosclerosis, Thrombosis, and Vascular Biology* **14**, 1829–1836.

Dinarello CA (1997) Proinflammatory and anti-inflammatory cytokines as mediators in the pathogenesis of septic shock. *Chest* **112**, 321S–329S.

Docke WD, Randow F, Syrbe U, Krausch D, Asadullah K, Reinke P, Volk HD & Kox W (1997) Monocyte deactivation in septic patients: restoration by IFN-gamma treatment. *Nature Medicine* **3**, 678.

Endres S, Ghorbani R, Kelley VE, Georgilis K, Lonnemann G, van der Meer JWM, Cannon JG, Rogers TS, Klempner MS, Weber PC, Schaefer EJ, Wolff SM & Dinarello CA (1989) The effect of dietary supplementation with *n*-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *New England Journal of Medicine* **320**, 265–271.

Friedman G, Silva E & Vincent JL (1998) Has the mortality of septic shock changed with time? *Critical Care Medicine* **26**, 2078–2086.

Fritsche KL, Shahbazian LM, Feng C & Berg JN (1997) Dietary fish oil reduces survival and impairs bacterial clearance in C3H/HEN mice challenged with *Listeria monocytogenes*. *Clinical Science* **92**, 95–101.

Gadek JE, DeMichele SJ, Karlstad MD, Pacht ER, Donahoe M, Albertson TE, Van Hoozen C, Wennberg AK, Nelson JL & Noursalehi Mand the Enteral Nutrition in ARDS Study Group (1999) Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. *Critical Care Medicine* **27**, 1409–1420.

Galban C, Montejo JC, Mesejo A, Marco P, Celaya S, Sanchez-Segura JM, Farre M & Bryg DJ (2000) An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. *Critical Care Medicine* **28**, 643–648.

Gavino VC & Gavino GR (1992) Adipose hormone-sensitive lipase preferentially releases polyunsaturated fatty acids from triglyerides. *Lipids* **27**, 950–954.

Grimminger F, Dürr U & Seeger U (1992) Ligand-operated synthesis of 4-series and 5-series leukotrienes in human neutrophils: critical dependence on exogenous free fatty acid supply. *Molecular Pharmacology* **41**, 757.

Grimminger F, Mayer K, Kiss L, Wahn H, Walmrath D, Bakhdi S & Seeger W (1997*a*) Synthesis of 4- and 5-series leukotrienes in the lung microvasculature challenged with *Escherichia coli* hemolysin: Critical dependence on exogenous free fatty acid supply. *American Journal of Respiratory Cell Molecular Biology* **16**, 317–324.

Grimminger F, Mayer K, Kiss L, Walmrath D & Seeger W (2000) PAF-induced synthesis of tetraenoic and pentaenoic leukotrienes in a model of pulmonary microvascular leukostasis. *American Journal of Physiology (Lung Cellular and Molecular Physiology)* **278**, L268–L275.

Grimminger F, Mayer K, Krämer H-J, Stevens J, Walmrath D & Seeger W (1993) Differential vasoconstrictor potencies of free fatty acids in the lung vasculature: 2- versus 3-series prostanoid generation. *Journal of Pharmacology and Experimental Therapeutics* **267**, 259–265.

Grimminger F, Wahn H, Krämer H-J, Stevens J, Mayer K, Walmrath D & Seeger W (1995) Differential influence of arachidonic versus eicosapentaenoic acid on experimental

pulmonary hypertension - relation to TxA2- versus TxA3-generation. *American Journal of Physiology* **268**, H2252–H2259, (Heart Circ. Physiol.).

Grimminger F, Wahn H, Mayer K, Kiss L, Walmrath D, Bahkdi S & Seeger W (1997*b*) Arachidonic acid increases, but eicosapentaenoic acid decreases exotoxin induced lung vascular leakage — relation to 4-series versus 5-series leukotriene generation. *American Journal of Respiratory Critical Care Medicine* **155**, 513–519.

Guidet B, Plot O, Masliah J, Barakett V, Maury E, Bereziat G & Offenstadt G (1996) Secretory non-pancreatic phospholipase A2 in severe sepsis: relation to endotoxin, cytokines and thromboxane B2. *Infection* **24**, 103–108.

Hammarström S, Hamberg M, Samuelsson B, Duell E, Stawski M & Voorhees JJ (1975) Increased concentrations of non-esterified arachidonic acid, 12L-hydroxyeicosatetraenoic acid, prostaglandin E_2 and prostaglandin F_{2alpha} in the epidermis of psoriasis. *Proceedings of the National Academy of Sciences USA* **72**, 5130.

Heller A, Koch T, Schmeck J & van Ackern K (1998) Lipid mediators in inflammatory disorders. *Drugs* **55**, 487–496.

Jaume JC, Mendel CM, Frost PH, Greenspan FS & Laufhton CW (1996) Extremely low doses of heparin release lipase activity into the plasma and can thereby cause artifactual elevations in the serum-free thyroxine concentration as measured by equilibrium dialysis. *Thyroid* **6**, 79–83.

Kox WJ, Bone RC, Krausch D, Docke WD, Kox SN, Wauer H, Egerer K, Querner S, Asadullah K, von Baehr R & Volk HD (1997) Interferon gamma-1b in the treatment of compensatory anti-inflammatory response syndrome. A new approach: proof of principle. *Archives of Internal Medicine* **157**, 389–393.

Kragballe K, Voorhees JJ & Goetzl EJ (1987) Inhibition by leukotriene B_5 of leukotriene B_4-induced activation of human keratinocytes and neutrophils. *Journal of Investigative Dermatology* **88**, 555.

Lovegrove JA, Brooks CN, Murphy MC, Gould BJ & Williams CM (1997) Use of manufactured foods enriched with fish oil as a means of increasing long-chain *n*-3 polyunsaturated fatty acid intake. *British Journal of Nutrition* **78**, 223–236.

Mancuso P, Whelan J, DeMichele SJ, Snider CC, Guszcza JA, Claycombe KJ, Smith GT, Gregory TJ & Karlstad MD (1997*a*) Effects of eicosapentaenoic and γ-linolenic acid on lung permeability and alveolar macrophage eicosanoid synthesis in endotoxic rats. *Critical Care Medicine* **25**, 523–532.

Mancuso P, Whelan J, DeMichele SJ, Snider CC, Guszcza JA & Karlstad MD (1997*b*) Dietary fish oil and fish oil and borage oil suppress intrapulmonary pro-inflammatory eicosanoid biosynthesis and attenuate pulmonary neutrophil accumulation in endotoxic rats. *Critical Care Medicine* **25**, 1198–1206.

May CL, Southworth AJ & Calder PC (1993) Inhibition of lymphocyte protein kinase C by unsaturated fatty acids. *Biochemical and Biophysical Research Communications* **195**, 823–828.

Mayer K, Fegbeutel C, Sibelius U, Krämer HJ, Hattar K, Seeger W & Grimminger F (1998*a*) Parenteral nutrition with *n*-6 vs. *n*-3-fatty acid-based lipid emulsions in septic patients - effects on plasma free fatty acids and lipid mediator generation. *American Journal of Respiratory and Critical Care Medicine* **157**, A99, (abstr).

Mayer K, Seeger W & Grimminger F (1998*b*) Clinical use of lipids to control inflammatory disease. *Current Opinion in Clinical Nutrition and Metabolic Care* **1**, 179–184.

Meerschaert J & Furie MB (1994) Monocytes use either CD11/CD18 or VLA-4 to migrate across human endothelium *in vitro*. *Journal of Immunology* **152**, 1915–1926.

Muller WA, Weigl SA, Deng X & Phillips DM (1993) PECAM-1 is required for transendothelial migration of leukocytes. *Journal of Experimental Medicine* **178**, 449–460.

Murray MJ, Kumar M, Gregory TJ, Banks PL, Tazelaar HD & DeMichele SJ (1995) Select dietary fatty acids attenuate cardiopulmonary dysfunction during acute lung injury in pigs. *American Journal of Physiology* **269**, H2090–H2099.

Murray MJ, Svingen BA, Holman RT & Yaksh TL (1991) Effects of a fish oil diet on pig's cardiopulmonary response to bacteremia. *Journal of Parenteral and Enteral Nutrition* **15**, 152–158.

Murray MJ, Svingen BA, Yaksh TL & Holman RT (1993) Effects of endotoxin on pigs prefed omega-3 vs. omega-6 fatty acids-enriched diets. *American Journal of Physiology* **265**, E920–E927.

Peterson J, Bihain BE, Bengtsson-Olivecrona G, Deckelbaum RJ, Carpentier YA & Olivecrona T (1990) Fatty acid control of lipoprotein lipase: A link between energy metabolism and lipid transport. *Proceedings of the National Academy of Sciences USA* **87**, 909.

Pscheidl E, Reisch S & Rugheimer E (1994) Chemically defined structured lipids with w-3 fatty acids maintain splanchic blood flow in a low-dose continuous endotoxin model. *Infusionstherapie und Transfusionsmedizin* **21**, 380–387.

Quinlan GJ, Lamb N, Tilley R, Evans TM & Gutteridge JMC (1997) Plasma hypoxantine levels in ARDS: implications for morbidity and mortality. *American Journal of Respiratory Critical Care Medicine* **155**, 479–484.

Robin AP, Askanazi J, Greenwood MRC, Carpentier YA, Gump FE & Kinney JM (1981) Lipoprotein lipase activity in surgical patients. Influence of trauma and sepsis. *Surgery* **90**, 401–408.

Rustan AC, Hustvedt BE & Drevon CA (1998) Postprandial decrease in plasma unesterified fatty acids during *n*-3 fatty acid feeding is not caused by accumulation of fatty acids in adipose tissue. *Biochimica et Biophysica Acta* **1390**, 245–257.

Samra JS, Simpson EJ, Clark LM, Forster CD, Humphreys SM, MacDonald LA & Frayn KN (1996) Effects of epinephrine infusion on adipose tissue: interactions between blood flow and lipid metabolism. *American Journal of Physiology* **34**, E834–E839.

Sane S, Baba M, Kusano C, Shirao K, Andoh T, Kamada T & Aikou T (2000) Eicosapentaenoic acid reduces pulmonary edema in endotoxemic rats. *Journal of Surgical Research* **93**, 21–27.

Solomkin JS, Cotta LA, Brodt JK, Hurst JW & Ogle CK (1984) Neutrophil dysfunction in sepsis III. Degranulation as a mechanism for nonspecific deactivation. *Journal of Surgical Research* **36**, 407–412.

Solomkin JS, Jenkins MK, Nelson RD, Chenoweth D & Simmons RL (1981) Neutrophil dysfunction in sepsis II. Evidence for the role of complement activation products in cellular deactivation. *Surgery* **90**, 319–327.

Sperling RI, Benincaso AI, Knoell CT, Larkin JK, Austen KF & Robinson DR (1993) Dietary omega-3 polyunsaturated fatty acids inhibit phophoinositide formation and chemotaxis in neutrophils. *Journal of Clinical Investigation* **91**, 651–660.

Spertini O, Luscinskas FW, Gimbrone MA Jr. & Tedder TF (1992) Monocyte attachment to activated human vascular endothelium in vitro is mediated by leukocyte adhesion molecule-1 (L-selectin) under nonstatic conditions. *Journal of Experimental Medicine* **175**, 1789–1792.

Suter PM & Ricou B (1998) Cytokines and lung injury. *Update in Intensive Care and Emergency Medicine* **30**, 41–53.

Terano T, Shiina T & Tamura Y (1996) Eicosapentaenoic acid suppressed the proliferation of vascular smooth muscle cells through modulation of various steps of growth signals. *Lipids* **31**, S301–S304.

Unterberg A, Wahl M, Hammersen F & Baethmann A (1987)

Permeability and vasomotor response of celebral vessels during exposure to arachidonic acid. *Acta Neuropathology* **73**, 209.

Volk HD, Reinke P & Döcke WD (2000) Clinical aspects: from systemic inflammation to immunoparalysis. *Chemical Immunology* **74**, 162–177.

Wallace FA, Miles EA & Calder PC (2000) Activation state alters the effect of dietary fatty acids on pro-inflammatory mediator production by murine macrophages. *Cytokine* **12**, 1374–1379.

Weber C, Erl W, Pietsch A, Danesch U & Weber PC (1995) Docosahexaenoic acid selectively attenuates induction of vascular cell adhesion molecule-1 and subsequent monocytic cell adhesion to human endothelial cells stimulated by tumor necrosis factor-α Arteriosclerosis. *Thrombosis, and Vascular Biology* **15**, 622–628.

Weber C & Springer TA (1998) Interaction of very late antigen-4 with VCAM-1 supports transendothelial chemotaxis of monocytes by facilitating lateral migration. *Journal of Immunology* **161**, 6825–6834.

Weissman C (1990) The metabolic response to stress: an overview and update. *Anesthesiology* **73**, 308–327.

Wheeler AP & Bernard GR (1999) Treating patients with severe sepsis. *New England Journal of Medicine* **340**, 207–214.

Yao YM, Redl H, Bahrami S & Schlag G (1998) The inflammatory basis of trauma/shock-associated multiple organ failure. *Inflammation Research* **47**, 201–210.