Proceedings of the Nutrition Society (2006), **65**, 264–277 DOI:10.1079/PNS2006500
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A Satellite Symposium sponsored by B. Braun Medical was held at The International Centre, Telford on 16 November 2005

Satellite Symposium on 'Fish oils: a parenteral perspective'*

Use of fish oil in parenteral nutrition: rationale and reality

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Excessive or inappropriate inflammation and immunosuppression are components of the response to surgery, trauma, injury and infection in some individuals and can lead, progressively, to sepsis and septic shock. The hyperinflammation is characterised by the production of inflammatory cytokines, arachidonic acid-derived eicosanoids and other inflammatory mediators, while the immunosuppression is characterised by impairment of antigen presentation and of T-helper lymphocyte type-1 responses. Long-chain *n*-3 fatty acids from fish oil decrease the production of inflammatory cytokines and eicosanoids. They act both directly (by replacing arachidonic acid as an eicosanoid substrate and by inhibiting arachidonic acid metabolism) and indirectly (by altering the expression of inflammatory genes through effects on transcription factor activation). Thus, long-chain *n*-3 fatty acids are potentially useful anti-inflammatory agents and may be of benefit in patients at risk of hyperinflammation and sepsis. As a consequence, an emerging application for *n*-3 fatty acids, in which they may be added to parenteral (or enteral) formulas, is in surgical or critically-ill patients. Parenteral nutrition that includes *n*-3 fatty acids appears to preserve immune function better than standard formulas and appears to diminish the extent of the inflammatory response. Studies to date are suggestive of clinical benefits from these approaches, especially in patients post surgery, although evidence of clinical benefit in patients with sepsis is emerging.

Fish oil: Inflammation: Immune function: Parenteral nutrition: Sepsis

Alterations in the inflammatory and immune responses occur as part of the host response to insult

The body's response to insults such as infection, surgery and injury includes an activation of some components of the immune system. The result is the local release of chemical mediators and the appearance of increased concentrations of some of these mediators in the bloodstream. The mediators released include eicosanoids, cytokines, reactive oxygen (superoxide anions, H_2O_2) and nitrogen (NO) species and platelet-activating factor; collectively, these mediators are known as inflammatory mediators and the process that produces them is termed the inflammatory response. Some of the inflammatory mediators are involved in direct destruction of pathogens, while others play a regulatory role within the immune or whole-body responses to insult (Fig. 1). The overall aims of the inflammatory response appear to be the creation of an environment characterised by oxidative stress and inflammation that is hostile to pathogens and the initiation of cellular immune responses involved in pathogen elimination (Fig. 1). Some components of the inflammatory response, such as IL-1β, induce cell-mediated immunity through the activation of T lymphocytes.

Although the inflammatory response has evolved to be protective and is clearly essential for host defence against pathogens, the host can be damaged by inappropriate, excessive or untimely production of inflammatory mediators. The body possesses antioxidant defences and is able to produce anti-inflammatory mediators in order to counter excessive oxidative stress and inflammation. Nevertheless, the balance between those conditions that are favourable

*This symposium was not part of the main programme of the Annual Meeting of the Nutrition Society and the British Association for Parenteral and Enteral Nutrition held at The International Centre, Telford on 16–17 November 2005.

Abbreviations: LT, leukotriene; MCT, medium-chain triacylglycerols; PG, prostaglandin; TX, thromboxane.

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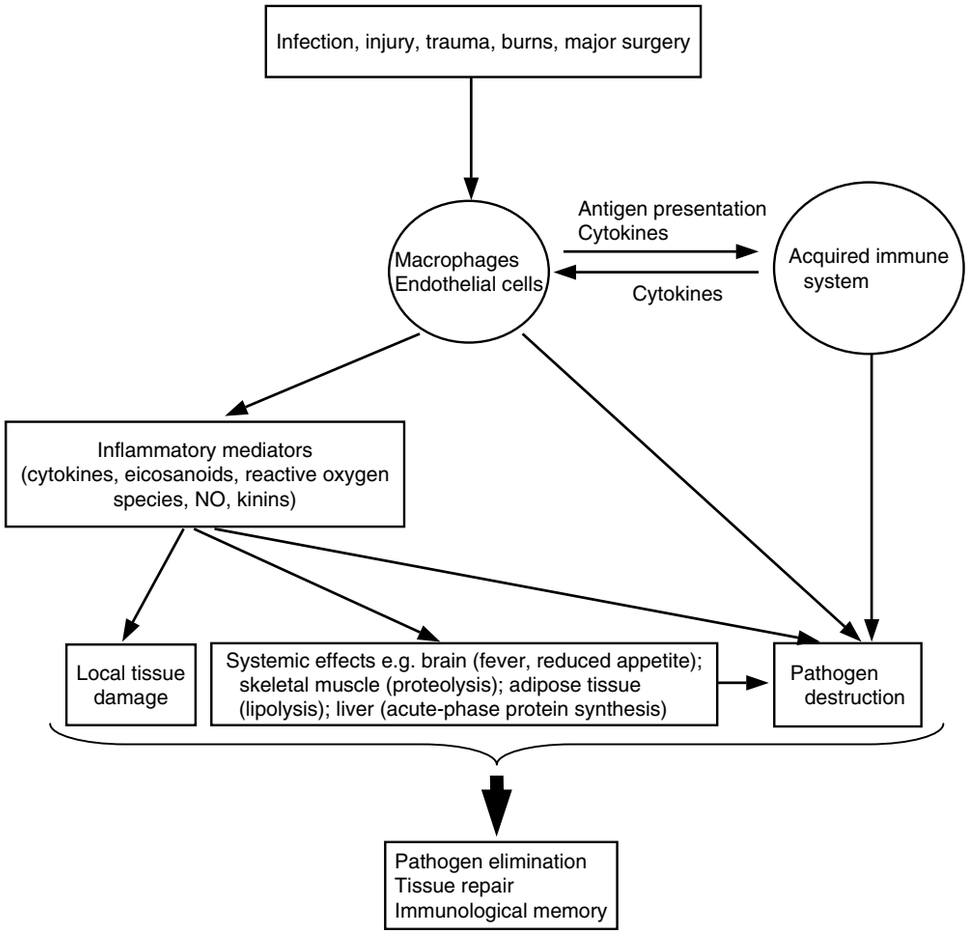

Fig. 1. The role of the inflammatory response in host defence. (Modified from Calder, 2001*b*, with permission from the American Oil Chemists' Society.)

to the host and those that are not favourable to the host can be lost, and this imbalance can have a major impact on patient outcome. The uncontrolled inflammatory response to insult (e.g. surgery, trauma, burns) is termed the systemic inflammatory response syndrome and involves excessive production of inflammatory cytokines, particularly TNF-α, IL-1β, IL-6 and IL-8 (Bone *et al*. 1997). Sepsis is the presence of systemic inflammatory response syndrome in response to, or in combination with, an infection (Bone *et al*. 1997). The mortality risk of sepsis is about 20%, and it predisposes to organ failure, which carries an elevated mortality risk. Septic shock is the occurrence of multiple organ failures, metabolic acidosis and hypotension, and it carries a mortality risk of 40–80% (Bone *et al*. 1997). Together systemic inflammatory response syndrome, sepsis and septic shock are termed 'septic syndromes', and they are the leading cause of death in critically-ill patients in Western countries. In the USA it has been estimated that in 1995 there were >750 000 cases of sepsis, with a 28·6% mortality rate (215 000 deaths) and a total cost of approximately US$ 17×10^9 (Angus *et al*. 2001).

Animal studies suggest a central role for inflammatory cytokines in the septic response. Mice injected with bacterial endotoxin (also termed lipopolysaccharide) exhibit high circulating concentrations of TNF-α, IL-1β, IL-6 and IL-8, and survival of these animals can be improved by administering anti-cytokine antibodies (Beutler *et al*. 1985; Tracey *et al*. 1987), cytokine receptor antagonists (Alexander *et al*. 1991) or anti-inflammatory cytokines such as IL-10 (Marchant *et al*. 1994), or by knocking out the TNF-α receptor (Pfeffer *et al*. 1993). Patients with sepsis show markedly elevated circulating concentrations of TNF-α, TNF receptor 1, IL-1β and IL-6, and the patients with the highest concentrations are more likely to die (Girardin *et al*. 1988; Arnalich *et al*. 2000; Hatherill *et al*. 2000). In addition, circulating leucocytes from patients with sepsis have high levels of activated NF-κB, a transcription factor that promotes the expression of numerous genes associated with inflammation, and again levels of activated NF-κB are higher in those patients who go on to die (Arnalich *et al*. 2000). Although Vervloet *et al*. (1998) state that 'these mediators [i.e. inflammatory cytokines] are largely, if not completely, responsible for the clinical signs and symptoms of the septic response to bacterial infection', other mediators are involved in the pathological processes that accompany critical illness. For example, prostaglandin (PG) E_2 is implicated in sepsis,

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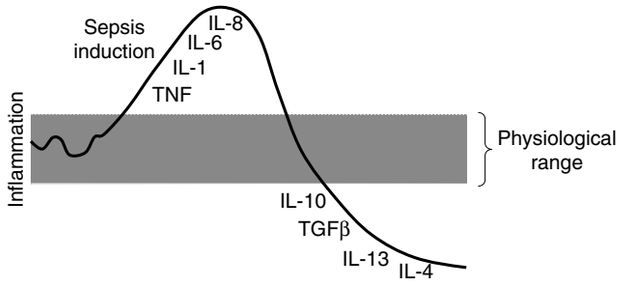

Fig. 2. Hypothetical biphasic immuno-inflammatory response to a traumatic insult. In sepsis the immunosuppressed phase lags behind the hyperinflammatory phase, i.e. initially, sepsis is characterised by increased generation of inflammatory mediators, but as it persists there is a shift towards an anti-inflammatory immunosuppressed state. TGF, transforming growth factor. (Modified from Calder, 2004, with permission from the American Oil Chemists' Society.)

burns and critical illness (Grbic *et al*. 1991; Ertel *et al*. 1992), while leukotriene (LT) B_4 and oxidants released by neutrophils are involved in acute respiratory distress syndrome (Kollef & Schuster, 1995).

In addition to hyperinflammation, patients with sepsis also display immunosuppression (Meakins *et al*. 1977; Lederer *et al*. 1999; Oberholzer *et al*. 2001). Lymphocytes from patients with sepsis, burns or trauma show impaired proliferation and produce low levels of the T-helper 1-type cytokines (e.g. interferon-γ) associated with host defence against bacteria and viruses, but high levels of the T-helper 2-type and regulatory T-cell-type cytokines (IL-4, IL-10) associated with inhibition of the host defence against bacteria and viruses (O'Sullivan *et al*. 1995; Heidecke *et al*. 1999; Lederer *et al*. 1999; Pellegrini *et al*. 2000). There also appears to be decreased monocyte expression of human leucocyte antigens (the proteins involved in antigen presentation to T-cells; Hershman *et al*. 1990; Wakefield *et al*. 1993; Astiz *et al*. 1996; Manjuck *et al*. 2000), which is associated with impaired ability of monocytes to stimulate T-cells (Manjuck *et al*. 2000). The traditional view is that the immunosuppressed phase of sepsis lags behind the hyperinflammatory phase (Fig. 2), i.e. initially, sepsis is characterised by increased generation of inflammatory mediators, but as it persists there is a shift towards an anti-inflammatory immunosuppressed state sometimes termed the compensatory anti-inflammatory response syndrome. However, some studies challenge this concept and suggest that the hyperinflammatory and immunosuppressed states may co-exist (Heidecke *et al*. 1999; Weighardt *et al*. 2000; Tschaikowsky *et al*. 2002).

n-6 PUFA, inflammation and immunity

Human immune and inflammatory cells are rich in PUFA, especially the *n*-6 PUFA linoleic acid and arachidonic acid, which together comprise about 30% of the fatty acids present (Gibney & Hunter, 1993; Yaqoob *et al*. 2000). Cell-culture-based studies with human endothelial cells have suggested that linoleic acid may play a role in inflammation through activation of NF-κB and increased production of TNF-α, IL-6 and other inflammatory mediators (Hennig *et al*. 1996, 2000; Toborek *et al*. 1997, 2002; Young *et al*. 1998; Park *et al*. 2001; Dichtl *et al*. 2002). Arachidonic acid also activates NF-κB in a monocytic cell line (Camandola *et al*. 1996), and induces TNF-α, IL-1α and IL-1β in osteoblasts (Priante *et al*. 2002) and IL-6 in macrophages (Bagga *et al*. 2003) and osteoblasts (Bordin *et al*. 2003). Arachidonic acid is also the principal substrate for cyclooxygenase and lipoxygenase enzymes, giving rise to 2-series PG and thromboxanes (TX) or 5-hydroxyeicosatetraenoic acids and 4-series LT respectively. These mediators, especially PGE_2 and the 4-series LT, have well-recognised roles in inflammation and immunity (Kinsella *et al*. 1990; Lewis *et al*. 1990; Tilley *et al*. 2001). For example, PGE_2 induces fever, increases vascular permeability and causes pain. LTB_4 increases vascular permeability, is a potent leucocyte chemoattractant, induces release of lysosomal enzymes and reactive oxygen species by neutrophils and induces production of TNF-α, IL-1β and IL-6. Arachidonic acid-derived mediators thus contribute to the inflammatory process and these roles most likely underpin their association with critical illness (Grbic *et al*. 1991; Ertel *et al*. 1992; Kollef & Schuster, 1995). Studies using the isolated perfused rabbit lung have identified key pathological roles for arachidonic acid-derived eicosanoids. Infusion of *Escherichia coli* haemolysin causes hypertension mediated by TXB_2 and increases vascular leakage mediated by 4-series LT (Grimminger *et al*. 1997*a*). Inclusion of arachidonic acid in the perfusate increases TXB_2 and 4-series LT generation and increases arterial pressure and vascular leakage (Grimminger *et al*. 1997*a*,*b*).

In addition to contributing to inflammatory processes PGE_2 acts to suppress cell-mediated immunity through the inhibition of both T-lymphocyte proliferation (Calder *et al*. 1992) and the production of the T-helper 1-type cytokines IL-2 and interferon-γ (Betz & Fox, 1991; Snijdewint *et al*. 1993; Katamura *et al*. 1995; Hilkens *et al*. 1996; Miles *et al*. 2003).

Thus, it is possible that an excessive supply of *n*-6 PUFA could act to promote, or at least exacerbate, states of inflammation and of immunosuppression. This situation could occur particularly in patients who are critically ill, have suffered a traumatic insult or burns, or have undergone major surgery, since such patients are at risk of developing systemic inflammatory response syndrome and compensatory anti-inflammatory response syndrome. Parenteral nutrition may be indicated for these categories of patient, particularly if the gastrointestinal tract is not fully functional. Lipids were introduced into parenteral nutrition formulas in the 1960s in order to provide a more balanced supply of energy, along with glucose (Edgren & Wretlind, 1963; Hallberg *et al*. 1966; Wretlind, 1972). The lipid typically used in parenteral nutrition is soyabean oil, in which linoleic acid comprises about 50% of the fatty acids present. A meta-analysis of total parenteral nutrition has suggested that the inclusion of lipids might be detrimental (lipids *v*. no lipids, $P = 0{\cdot}09$; Heyland *et al*. 1998), at least in very-ill patients; in most of the studies included in the meta-analysis soyabean oil-based lipid emulsions were used. A recent study in patients following major

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gastrointestinal surgery (Koch & Heller, 2005) has identified that the amount of *n*-6 PUFA infused is one of two predictors of the length of hospital stay (which increases by 1·6 d/100 g *n*-6 PUFA infused), the other predictor is the delay in the onset of initiating nutritional support. Some *in vitro* experiments have shown that soyabean oil-based lipid emulsions can exert immunosuppressive effects (for references, see Calder *et al*. 1994), which would clearly be detrimental in patients at risk of infection and sepsis. Clinical trials with soyabean oil-based lipid emulsions provide conflicting evidence, with some showing selective immunosuppressive effects (Monson *et al*. 1988; Battistella *et al*. 1997; Furukawa *et al*. 2002), perhaps linked to poorer patient outcomes (Battistella *et al*. 1997). However, other studies do not show such effects on the immune system (Dionigi *et al*. 1985; Gogos *et al*. 1990; Sedman *et al*. 1991) or on clinical outcomes (Lenssen *et al*. 1998). Details of these studies are given in Table 1. Nevertheless, there is a view developing that the use of lipid emulsions based entirely on soyabean oil in parenteral nutrition may not be optimal or may even be harmful. The concern about potential harm, the view of sepsis as a hyper-inflammatory state followed by an immunosuppressed state (Fig. 2) and the idea that *n*-6 PUFA might be 'pro-inflammatory and immunosuppressive' have led to the development of alternative lipid emulsions for parenteral applications. Two approaches to decreasing the amount of linoleic acid present in the emulsion have been to partly replace soyabean oil with triacylglycerols rich in medium-chain saturated fatty acids (termed medium-chain triacylglycerols; MCT) or with olive oil. These approaches will not be discussed further here, but further information may be found elsewhere (Ulrich *et al*. 1996; Adolph, 1999).

Fish oil, inflammation and immunity

The use of MCT or olive oil in parenteral nutrition results in decreased linoleic acid administration. However, there is a view that *n*-6 PUFA : *n*-3 PUFA in lipid emulsions should be decreased (Furst & Kuhn, 2000; Adolph, 2001; Grimble, 2005; Grimm, 2005), and this objective is not achieved with MCT or olive oil since neither of these components contains major amounts of *n*-3 PUFA. Using fish oil, which contains the long-chain *n*-3 PUFA EPA and DHA, to partly replace soyabean oil offers the possibility of decreasing both the amount of linoleic acid present and the *n*-6 PUFA : *n*-3 PUFA of lipid emulsions. This option is especially attractive because not only is the supply of linoleic acid decreased, but the long-chain *n*-3 PUFA are themselves anti-inflammatory (for reviews, see Calder, 2001*a*,*b*, 2002, 2003, 2005). Consumption of fish oil results in increased amounts of EPA and DHA, partly at the expense of arachidonic acid, in cells involved in immunity and inflammation (see Calder, 2001*a*). The functional importance of this outcome is that it decreases the amount of arachidonic acid available as a substrate for eicosanoid synthesis. In addition, EPA and DHA competitively inhibit the metabolism of arachidonic acid by cyclooxygenase and 5-lipoxygenase. Through these actions fish oil supplementation of the human diet has been shown to result in decreased production of PGE_2, TXB_2, LTB_4, 5-hydroxyeicosatetraenoic acid and LTE_4 by inflammatory cells (Lee *et al*. 1985; Endres *et al*. 1989; Meydani *et al*. 1993; Sperling *et al*. 1993; von Schacky *et al*. 1993; Caughey *et al*. 1996; Trebble *et al*. 2003*b*). EPA can also act as a substrate for cyclooxygenase and lipoxygenase enzymes, giving rise to a different family of eicosanoids, i.e. the 3-series PG and TX, the 5-series LT and the hydroxyeicosapentaenoic acids. Thus, fish oil supplementation of the human diet has been shown to result in increased production of LTB_5, LTE_5 and 5-hydroxy-eicosapentaenoic acid by inflammatory cells (Lee *et al*. 1985; Sperling *et al*. 1993; von Schacky *et al*. 1993), although generation of PGE_3 has been more difficult to demonstrate (Hawkes *et al*. 1991). The mediators formed from EPA are frequently less potent than those formed from arachidonic acid. For example, LTB_5 is 10-fold to 100-fold less potent as a neutrophil chemotactic agent than LTB_4 (Goldman *et al*. 1983; Lee *et al*. 1984, 1988). A recent study (Bagga *et al*. 2003) has reported that PGE_3 is less potent than PGE_2 at inducing cyclooxygenase-2 gene expression in fibroblasts and IL-6 production by macrophages. Studies using the isolated rabbit lung perfused with *E. coli* haemolysin (Grimminger *et al*. 1997*a*,*b*) have identified contrasting effects of arachidonic acid- and EPA-derived eicosanoids. While arachidonic acid infusion increases TXB_2 and 4-series LT generation, arterial pressure and vascular leakage (Grimminger *et al*. 1997*a*,*b*), the inclusion of EPA in the perfusate decreases TXB_2 and 4-series LT generation, decreases arterial pressure and vascular leakage, and increases the generation of TXB_3 and 5-series LT (Grimminger *et al*. 1997*a*). Perfusion with fish oil also attenuates the hypertension (Breil *et al*. 1996) and the increased vascular permeability and oedema (Koch *et al*. 1995) induced by Ca ionophore. These effects are associated with decreased production of LTC_4 and TXB_2 and markedly increased production of LTC_5 (Koch *et al*. 1995; Breil *et al*. 1996).

In addition to the modulation of eicosanoid generation from arachidonic acid and to EPA acting as a substrate for an alternative family of eicosanoids, recent studies (for reviews, see Serhan 2004, 2005) have identified a novel group of anti-inflammatory mediators, termed resolvins, formed from EPA and DHA.

n-3 PUFA from fish oil have also been shown to alter the production of inflammatory cytokines. EPA does not activate NF-κB in a monocytic cell line (Camandola *et al*. 1996), while both EPA and DHA inhibit endotoxin-stimulated production of IL-6 and IL-8 by cultured human endothelial cells (de Caterina *et al*. 1994; Khalfoun *et al*. 1997). More recent studies have shown that: (1) EPA does not induce TNF-α, IL-1α or IL-1β (Priante *et al*. 2002) or IL-6 (Bordin *et al*. 2003) in osteoblasts, and even counters the up regulating effect of arachidonic acid (Priante *et al*. 2002); (2) EPA and DHA can totally abolish cytokine-induced up-regulation of TNF-α, IL-1α and IL-1β in cultured bovine chondrocytes and in human osteoarthritic cartilage explants (Curtis *et al*. 2000, 2002); (3) EPA or fish oil inhibit endotoxin-induced TNF-α production by monocytes (Lo *et al*. 1999; Babcock *et al*. 2002; Novak

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Table 1. Some reported immunological and clinical outcomes of studies using lipid emulsions based entirely on soyabean oil

Patient characteristics	Parenteral nutrition used	Duration	Immuno-inflammatory and clinical outcomes measured	Effects observed	Reference
Undernourished patients undergoing surgery for gastric or oesophageal cancer	No lipid *v.* soyabean oil	Daily for 2 weeks before surgery and then for 1 week after surgery	Nos. of blood granulocytes, lymphocytes, T-cells and B-cells	Granulocyte nos. increased at week 3 in soyabean oil group; total lymphocytes decreased (approximately 50%) at week 3 in the no-lipid group	Dionigi *et al.* (1985)
			Serum IgG and IgM concentrations	None	
			Leucocyte chemotaxis	None	
			Granulocyte adherence to nylon	Decreased (approximately 30%) at week 3 in the no-lipid group	
			Granulocyte phagocytosis	None	
Malnourished patients undergoing surgery for gastrointestinal cancer	Soyabean oil	For 7d before surgery	Natural killer cell activity of PBMNC	Decreased (approximately 50%) at day 7	Monson *et al.* (1988)
			T-cell proliferation in response to mitogen	None	
			IL-2 production by T-cells in response to mitogen	None	
			Cytotoxicity of IL-2 activated PBMNC	Decreased (approximately 50%)	
Malnourished seriously-ill patients	No lipid *v.* soyabean oil; Soyabean oil *v.* MCT–soyabean oil (50:50, v/v)	10 d	Nos. of blood T-cell, helper T-cell, suppressor T-cell	Helper:suppressor cells decreased (approximately 20%) in the soyabean oil group	Gogos *et al.* (1990)
			Nos. of blood natural killer cells	Absolute no. and percentage of natural killer cells decreased (approximately 5–10%) in the no-lipid group	
Malnourished patients undergoing surgery for gastrointestinal cancer	No lipid *v.* soyabean oil *v.* MCT–soyabean oil (50:50, v/v)	For 7d before surgery	Natural killer cell activity of PBMNC	Increased (approximately 30%) in the MCT–soyabean oil group	Sedman *et al.* (1991)
			T-cell proliferation in response to mitogen	None	
			IL-2 production by T-cells in response to mitogen	Decreased (approximately 10%) in the no-lipid group; increased (approximately 35%) in the soyabean oil group	
			Cytotoxicity of IL-2 activated PBMNC	Decreased (approximately 35%) in the soyabean oil group; increased (approximately 15%) in the MCT–soyabean oil group	
Trauma patients	No lipid *v.* soyabean oil	10 d	Natural killer cell activity of PBMNC	Lower (approximately 65%) in the soyabean oil group	Battistella *et al.* (1997)
			Period on mechanical ventilation	Longer in the soyabean oil group (27 *v.* 15 d)	

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			No. of infections	Greater in the soyabean oil group (72 *v.* 39)	
			Length of intensive care unit stay	Longer in the soyabean oil group (29 *v.* 18 d)	
			Length of hospital stay	Longer in the soyabean oil group (39 *v.* 27 d)	
Patients undergoing bone-marrow transplantation	Low-dose soyabean oil *v.* standard soyabean oil	From 3 d before transplantation until oral energy intake >42 kJ (10 kcal)/kg for two successive days	Time to first blood infection	None	Lenssen *et al.* (1998)
			Types of bacteria cultured from blood	None	
			Types of fungi cultured from blood	None	
			Urinary tract infections	None	
			Lung infections	None	
Patients undergoing gastrointestinal or oesophageal surgery	No lipid *v.* soyabean oil	From 7 d before surgery until 14 d after surgery	Serum C-reactive protein concentrations	None	Furukawa *et al.* (2002)
			Serum IL-6 concentrations	None in unstressed patients, but IL-6 higher at 2 h and 1 d post-surgery in stressed patients in soyabean oil group	
			T-cell proliferation in response to mitogens	None in unstressed patients, but T-cell proliferation lower at day 7 post-surgery in stressed patients in the soyabean oil group	

MCT, medium-chain triacylglycerols; PBMNC, peripheral-blood mononuclear cells.

et al. 2003; Zhao *et al.* 2004). EPA is also less potent than arachidonic acid in inducing IL-6 expression by macrophages (Bagga *et al.* 2003). EPA prevents NF-κB activation by TNF-α in cultured pancreatic cells; an effect that involves decreased degradation of the inhibitory subunit of NF-κB, perhaps through decreased phosphorylation (Ross *et al.* 1999). Similarly, EPA or fish oil decrease endotoxin-induced activation of NF-κB in human monocytes (Lo *et al.* 1999; Novak *et al.* 2003; Zhao *et al.* 2004), which is associated with decreased phosphorylation of inhibitory subunit of NF-κB (Novak *et al.* 2003; Zhao *et al.* 2004), perhaps because of decreased activation of mitogen-activated protein kinases (Lo *et al.* 2000). These observations suggest direct effects of long-chain *n*-3 PUFA on inflammatory gene expression via inhibition of activation of the transcription factor NF-κB.

Animal feeding studies with fish oil support the observations made in cell culture in relation to the effects of long-chain *n*-3 PUFA on NF-κB activation and inflammatory cytokine production. Compared with feeding maize oil, fish oil lowers NF-κB activation in endotoxin-activated murine spleen lymphocytes (Xi *et al.* 2001). Feeding fish oil to mice decreases *ex vivo* production of TNF-α, IL-1β and IL-6 by endotoxin-stimulated macrophages (Billiar *et al.* 1988; Renier *et al.* 1993; Yaqoob & Calder, 1995) and decreases circulating TNF-α, IL-1β and IL-6 concentrations in mice injected with endotoxin (Sadeghi *et al.* 1999). Several studies in healthy human volunteers involving supplementation of the diet with fish oil have demonstrated decreased production of TNF-α, IL-1β and IL-6 by endotoxin-stimulated monocytes or mononuclear cells (a mixture of lymphocytes and monocytes; Endres *et al.* 1989; Meydani *et al.* 1991; Abbate *et al.* 1996; Caughey *et al.* 1996; Trebble *et al.* 2003*a*; Wallace *et al.* 2003).

Thus, an examination of fatty acid composition and eicosanoid profiles, cell- and tissue-culture work and animal and human feeding studies has revealed a range of anti-inflammatory actions of long-chain *n*-3 PUFA (Table 2). These anti-inflammatory actions may be of benefit in sepsis, particularly during the 'early' hyperinflammatory phase. The benefits of fish oil in animal models of experimental endotoxaemia have been clearly demonstrated. For example, dietary fish oil or fish oil infused intravenously markedly enhances the survival of guinea-pigs to intraperitoneal endotoxin when compared with safflower oil (Mascioli *et al.* 1988, 1989). Also, dietary fish oil results in a decreased concentration of circulating post-endotoxin eicosanoids (PGE_2, TXB_2, 6-keto-$PGF_{1\alpha}$ in rats and in decreased eicosanoid generation by alveolar macrophages (Utsunomiya *et al.* 1994; Sane *et al.* 2000). Furthermore, compared with dietary safflower oil, fish oil results in lower circulating TNF-α, IL-1β and IL-6 concentrations following endotoxin administration to mice (Sadeghi *et al.* 1999). Dietary fish oil also decreases sensitivity to exogenously-administered inflammatory cytokines (Pomposelli *et al.* 1990; Mulrooney & Grimble, 1993). Fish oil decreases endotoxin-induced metabolic perturbations in guinea-pigs and rats (Pomposelli *et al.* 1991; Teo *et al.* 1991), improves heart and lung function and decreases lung oedema in endotoxic rats (Mancuso

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Table 2. Summary of the anti-inflammatory effects of long chain *n*-3 PUFA (modified from Calder, 2004, with permission from the American Oil Chemists' Society)

Anti-inflammatory effect	Mechanism(s) involved
Decreased generation of arachidonic acid-derived eicosanoids (many with inflammatory actions)	Partial replacement of arachidonic acid in cell membrane phospholipids
	Inhibition of arachidonic acid metabolism by phospholipase A_2, COX and 5-LOX
	Decreased induction of COX-2, 5-LOX and 5-LOX activating protein
Increased generation of EPA-derived eicosanoids (many with less inflammatory actions than those derived from arachidonic acid)	Increased cell membrane phospholipid content of EPA
Increased generation of EPA- and DHA-derived resolvins (with anti-inflammatory actions)	Increased cell membrane phospholipid content of EPA and DHA
Decreased generation of inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8)	Decreased activation of NF-κB (via decreased phosphorylation of IκB)
	?Altered activity of other transcription factors*
	?Differential effects arachidonic acid *v.* EPA
	?Differential effects of arachidonic acid-derived eicosanoids *v.* EPA-derived eicosanoids
Decreased expression of adhesion molecules*	Decreased activation of NF-κB (via decreased phosphorylation of IκB);
	?Altered activity of other transcription factors

COX, cyclooxygenase; LOX, lipoxygenase; IκB, inhibitory subunit of NF-κB.
*Not discussed here (see Calder, 2002).

et al. 1997*a*,*b*; Murray *et al*. 2000; Sane *et al*. 2000) and pigs (Murray *et al*. 1991, 1993, 1995).

In addition to the effects on the production of inflammatory eicosanoids and inflammatory cytokines, long-chain *n*-3 PUFA also exert effects on cell-mediated immunity. Large amounts of fish oil in the diet of laboratory animals have been reported to exert immunosuppressive effects (for reviews, see Calder, 2001*b*; Calder *et al*. 2002). Clearly, such effects are to be avoided in patients with sepsis. However, studies in healthy human volunteers are equivocal, although recent human studies suggest that adverse immunological effects are not exerted at modest doses of fish oil (Yaqoob *et al*. 2000; Wallace *et al*. 2003; Miles *et al*. 2004) and one study reports that enhanced T-cell responses (proliferation and interferon-γ production) may occur at modest doses provided that antioxidants are also given (Trebble *et al*. 2003*b*). In terms of sepsis, the true test of immunocompetence occurs when live pathogens are administered. This situation is different from using endotoxin, which is not living and therefore does not require a robust cell-mediated immune response to eliminate it. As indicated earlier, it is clear that long-chain *n*-3 PUFA protect against the deleterious effects of endotoxins, and the same appears to be true for some live pathogens. The infusion of fish oil into rats also receiving low-dose endotoxin decreases the number of viable bacteria in mesenteric lymph nodes and the liver, and as fish oil does not decrease bacterial translocation across the gut, the conclusion drawn is that fish oil must have improved bacterial killing (Pscheidl *et al*. 2000). Compared with linoleic acid-rich vegetable oils, fish oil fed to rats before exposure to live bacteria (either as a result of caecal ligation and puncture or intravenous administration of live group B *Streptococcus*) results in increased survival, which is associated with decreased production of PGE_2 (Barton *et al*. 1991; Rayon *et al*. 1997). The infusion of fish oil after the induction of sepsis by caecal ligation and puncture decreases mortality (and PGE_2 production) when compared with vegetable oil (Lanza-Jacoby *et al*. 2001). Intragastric administration of fish oil into chow-fed rats before caecal ligation and puncture improves survival when compared with saline (9 g NaCl/l) or vegetable oil infusion (Johnson *et al*. 1993). Thus, the picture that emerges from a range of animal studies is that administration of long-chain *n*-3 PUFA in the form of fish oil increases survival on exposure to live pathogens. From this outcome it can be inferred that host immune defences are likely to have been improved by long-chain *n*-3 PUFA. Interestingly, several studies have focused on the fish oil-induced decrease in PGE_2 production as being a key mechanistic effect, suggesting that the immunosuppressive effect of PGE_2 generated in response to infection might be deleterious to host survival.

Use of fish oil in parenteral nutrition

Lipid emulsions that include fish oil have been used in clinical trials and some of these emulsions have subsequently become commercially available, at least in some countries. Omegaven®, produced by Fresenius Kabi (Bad Homberg, Germany), is a lipid emulsion (100 g lipid/l) that uses fish oil as the lipid source. Each 100 ml Omegaven® contains 2·7–5·9 g EPA + DHA (information supplied by the manufacturers). It is recommended that Omegaven® is used in combination with other emulsions (e.g. those based on soyabean oil or mixtures of MCT and soyabean oil) such that Omegaven® contributes 10–20 % of the infused emulsion. SMOFLipid® is also produced by Fresenius Kabi. It is a lipid emulsion (200 g lipid/l) in which the lipid is a mix of (g/100 g): 30, MCT; 30, soyabean oil; 25, olive oil; 15, fish oil. Lipoplus® (also known as Lipidem®

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in some countries), produced by B. Braun (Melsungen, Germany), is a lipid emulsion (200 g lipid/l) in which the lipid is a mix of (g/100 g): 50, MCT; 40, soyabean oil; 10, fish oil. Each 100 ml Lipoplus® contains 0·9–1·7 g EPA + DHA (information supplied by the manufacturers).

Studies in surgical patients

Intravenous infusion of a lipid emulsion containing fish oil into patients for 5 d following gastrointestinal surgery results in an altered fatty acid composition of leucocytes; EPA content is increased 2·5-fold (Morlion *et al*. 1996). This change would be expected to impact on the profile of eicosanoids produced from arachidonic acid and EPA. Indeed, several studies have demonstrated that intravenous infusion of lipid emulsions containing fish oil into patients who have undergone major gastrointestinal surgery results in lower production of arachidonic acid-derived LT (e.g. LTB_4, LTC_4) and TX (e.g. TXA_2) and higher production of EPA-derived LT (e.g. LTB_5, LTB_5-isomers, LTC_5) by blood leucocytes stimulated *ex vivo* (Morlion *et al*. 1996; Wachtler *et al*. 1997; Schulzki *et al*. 1999; Kelbel *et al*. 2002; Koller *et al*. 2003). Plasma TNF-α concentrations are lower at day 6 post surgery while plasma IL-6 concentrations are lower at day 10 post surgery in patients who have undergone major gastrointestinal surgery and then received a mix of MCT–soyabean oil–fish oil (50:30:20, by vol.; a prototype version of Lipoplus®) for 5 d post surgery compared with those who have received a MCT–soyabean oil mix (50:50, v/v; Wachtler *et al*. 1997). The study does not report clinical outcomes. A more recent study (Weiss *et al*. 2002) has infused Omegaven®, providing 10 g lipid (fish oil)/d, on the day before abdominal surgery and on days 1–5 following abdominal surgery. On days 4 and 5 the patients also received standard total parenteral nutrition that included 50 g fat as soyabean oil/d. It was found that TNF-α production by endotoxin-stimulated whole blood has a tendency to be lower (although not significantly) at post-operative day 5 in the fish oil group. Serum IL-6 concentrations were reported to be significantly lower at days 0, 1 and 3 in the fish oil group than in the controls. Monocyte expression of human leucocyte antigen-DR was shown to be preserved in the fish oil group, but to decline at post-surgery days 3 and 5 in the control group. No differences in infection rates or mortality were observed, although there was a tendency for post-operative stay in intensive care (4·1 d *v*. 9·1 d in the control group) and total hospital stay (17·8 d *v*. 23·5 d in the control group) to be shorter in the fish oil group. Post-operative stay on medical wards was found to be significantly shorter in the fish oil group ($P<0·05$). Another study (Schauder *et al*. 2002) has compared the effects of lipid-free total parenteral nutrition and parenteral nutrition including soyabean oil or a soyabean oil–fish oil mix (83:17, v/v; Omegaven®) for 5 d after large-bowel surgery. No differences between the groups were found in relation to the numbers of circulating lymphocytes, B lymphocytes, helper T lymphocytes, cytotoxic T lymphocytes or natural killer cells before surgery or at days 3 and 6 post surgery, although the numbers were affected by surgery itself. No differences between groups were found in relation to T-lymphocyte proliferation, but in the fish oil group IL-2 production was shown to be increased and the post-surgery decline in interferon-γ production prevented. Taken together, these studies indicate that the inclusion of fish oil in parenteral nutrition regimens for patients who have undergone gastrointestinal surgery modulates the generation of inflammatory eicosanoids (Morlion *et al*. 1996; Wachtler *et al*. 1997; Koller *et al*. 2003) and cytokines (Wachtler *et al*. 1997; Weiss *et al*. 2002) and may help to counter the surgery-induced decline in antigen-presenting cell activity (Weiss *et al*. 2002) and T-lymphocyte cytokine production (Schauder *et al*. 2002). Importantly, these studies do not reveal deleterious immunological effects of fish oil infusion in these patients. Furthermore, the only one of these fairly small studies to have examined hard end points such as length of hospital stay suggests real clinical benefit from fish oil infusion in these patients (Weiss *et al*. 2002). A more recent report (Tsekos *et al*. 2004) from a larger cohort of patients receiving parenteral nutrition post surgery does indicate the benefit of the inclusion of fish oil in the regimen. No differences were found between the control group (MCT–soyabean oil; 50:50, v/v) and the patients receiving fish oil (a mix of Omegaven® with the MCT–soyabean oil mix (50:50, v/v) such that a maximum of one-third of the mix was as fish oil) in relation to the percentage of patients who were reported to develop wound infections (6 for the fish oil group *v*. 11 for the control group) or who subsequently died (12 for the fish oil group *v*.15 for the control group), or in the length of hospital stay (25 d for the fish oil group *v*. 29 d for the control group). However, the percentage of patients in the fish oil group who were readmitted to intensive care (5) was found to be significantly lower ($P<0·05$) than that for the control group (17). A group of patients also received the fish oil-containing emulsion for 2 d pre-operatively. For this group a number of very significant benefits were found when compared with the control group: a significantly decreased need for mechanical ventilation (17% *v*. 31% respectively; $P<0·05$); a significantly shorter length of hospital stay (22 d *v*. 29 d respectively; $P<0·05$); significantly less need for readmission to intensive care (5% *v*. 17% respectively; $P<0·05$); a significantly lower mortality (3% *v*. 15% respectively; $P<0·05$; Tsekos *et al*. 2004). Another study (Heller *et al*. 2004) has revealed that intravenous infusion of a lipid emulsion containing soyabean oil–fish oil (80:20, v/v) into patients for 5 d following major gastrointestinal surgery accelerates normalisation of liver and pancreatic function compared with soyabean oil alone. Overall, no difference was found between the groups in relation to the length of stay in the intensive care unit or in hospital. However, in a subgroup of patients at risk of sepsis a reduced intensive care unit stay was reported in the patients receiving fish oil (4·0 d *v*. 5·3 d in the control group; $P=0·01$; Heller *et al*. 2004). In a recently published study (Koch & Heller, 2005) a mixed group of >650 patients, including about 230 post-surgery patients, received parenteral nutrition containing fish oil (Omegaven®) at 0·11 g/kg body weight per d for at least 3 d (mean 8·7 d). A significantly lower rate of infections ($P<0·0005$), fewer complications ($P<0·005$) and shorter

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length of hospital stay ($P=0{\cdot}05$) were reported for the post-surgery patients receiving fish oil compared with those receiving the control emulsion. Furthermore, infusion of about 0·15 g fish oil/kg body weight per d was found to decrease mean intensive care unit stay from 8·7 d to 5·3 d and hospital stay from 27·4 d to 25·5 d. Schulzki *et al.* (1999) have reported that infusion of a mix of MCT–soyabean oil–olive oil–fish oil (30:30:25:15, by vol.; SMOFLipid®) into patients on days 1–6 following surgery results in a significantly lower ($P<0{\cdot}05$) length of hospital stay (13·4 d) compared with patients receiving soyabean oil (20·4 d). In a study by Kelbel *et al.* (2002) post-surgery patients received soyabean oil or a soyabean oil–fish oil mix (80:20, v/v) for 5 d. It was found that the incidence of sepsis (14% *v.* 25% in the control group), deaths in the intensive care unit (7% *v.* 12·5% in the control group), the length of intensive care unit stay (2 d *v.* 5·5 d in the control group) and the length of hospital stay (18 d *v.* 23 d in the control group) have a tendency to be lower in the patients receiving fish oil, although the decrease is not significant. Wichmann *et al.* (2004) have reported the length of hospital stay for patients who after gastrointestinal surgery received a control emulsion (soyabean oil) or an emulsion that included MCT–soyabean oil–fish oil (50:40:10, by vol.; Lipoplus®). The length of stay was found to be significantly shorter ($P=0{\cdot}006$) in patients receiving fish oil (17·2 d) than in the control group (21·9 d).

Although the studies of Schulzki *et al.* (1999), Kelbel *et al.* (2002) and Wichmann *et al.* (2004) are encouraging, they have been published only in abstract form and further details of these studies are required for them to be evaluated more fully. Even without these details, findings available from published studies in patients undergoing gastrointestinal surgery clearly demonstrate clinical benefit from the inclusion of long-chain *n*-3 PUFA in parenteral nutrition regimens (Weiss *et al.* 2002; Heller *et al.* 2004; Tsekos *et al.* 2004; Koch & Heller, 2005). However, the study of Tsekos *et al.* (2004) also demonstrates a much greater benefit if the fatty acids are additionally provided pre-surgery, which is only possible in elective surgery. The greater benefit of pre-operative infusion of long-chain *n*-3 PUFA may relate to better incorporation of the fatty acids into leucocytes and other tissues.

Studies in patients with established sepsis

Infusion of a mix of soyabean oil–fish oil (Omegaven®; 66:33, v/v) over 5 d has been shown to decrease serum C-reactive protein concentration by an average of about 88% in patients with abdominal sepsis; parenteral soyabean oil alone was not found to alter C-reactive protein concentration (Grecu *et al.* 2003). In patients with sepsis who were intolerant of enteral nutrition and received a standard soyabean oil-based emulsion or an emulsion containing fish oil (Omegaven®) for 5 d (Mayer *et al.* 2003*a*) or 10 d (Mayer *et al.* 2003*b*) it was found that blood leucocyte counts and serum C-reactive protein concentration tend to be lower and production of LTB_5 by stimulated neutrophils is higher in patients receiving fish oil (Mayer *et al.* 2003*a*). Production of TNF-α, IL-1β, IL-6, IL-8 and IL-10 by endotoxin-stimulated mononuclear cells does not increase during infusion of the fish oil-containing emulsion, whereas production of the four proinflammatory cytokines is markedly elevated during the first 2 d of infusion of soyabean oil (Mayer *et al.* 2003*b*). These studies establish that infusion of long-chain *n*-3 PUFA into patients with sepsis can modulate inflammatory mediator production and related inflammatory processes. It has been demonstrated that this outcome might be associated with clinical improvements. Grecu *et al.* (2003) have reported significantly decreased re-operation rates (7% *v.* 31% in the control group), intensive care unit stay (3 d *v.* 9 d in the control group) and hospital stay (12 d *v.* 20 d in the control group) in patients receiving parenteral fish oil (soyabean oil–Omegaven® mix; 66:33, v/v) compared with those receiving soyabean oil, although no difference in mortality was found between the two groups (7–8% in both groups). Koch & Heller (2005), in their study of parenteral *n*-3 PUFA infusion that included 268 patients with abdominal sepsis, have reported a lower rate of infection and shorter lengths of intensive care unit and hospital stay in those patients receiving >0·05 g fish oil/kg body weight per d than in those receiving <0·05 g fish oil/kg body weight per d. Mortality was found to be significantly decreased in those patients who received >1 g fish oil/kg body weight per d (Koch & Heller, 2005). Thus, these recent data are strongly suggestive of genuine clinical benefit from the inclusion of long-chain *n*-3 PUFA in parenteral nutrition regimens given to patients with sepsis.

One other study that should be mentioned in this context is a study of enteral nutrition in patients with acute respiratory distress syndrome (Gadek *et al.* 1999), since this study also demonstrates clinical improvement following long-chain *n*-3 PUFA administration. In this study the control group of patients received an enteral formula in which the lipid source was maize oil–soyabean lecithin (97:3, v/v). The experimental formula was (%, v/v): 32, rapeseed oil; 25, MCT; 20, borage (*Borago officinalis*) oil; 20, fish oil; 3, soyabean lecithin. The experimental formula also contained more vitamin C and vitamin E than the control and it contained β-carotene, taurine and carnitine, which the control formula did not. Patients given the experimental formula for 6 d received (g/d) approximately: 7, EPA; 3, DHA; 6, γ-linolenic acid; 1·1, vitamin C; 0·4, vitamin E; 6·6 mg, β-carotene. By day 4 the numbers of total leucocytes and of neutrophils in the alveolar fluid were found to have declined markedly in the experimental group and to be lower than those in the control group. Arterial oxygenation and gas exchange were shown to have improved in patients in the experimental group, who had a decreased requirement for supplemental O_2, decreased time on ventilation support and a shorter length of stay in intensive care (12·8 d *v.* 17·5 d in the control group; $P=0{\cdot}016$). It was found that total length of hospital stay tended to be shorter in the experimental group (29·6 d *v.* 34·6 d in the control group; $P=0{\cdot}07$) and fewer patients developed new organ failure (four of fifty-one patients *v.* thirteen of forty-seven patients in the control group; $P=0{\cdot}015$). Mortality was reported to be 12% in the experimental group and 19% in the control group, although this difference was not significant ($P=0{\cdot}31$).

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More recently, new data from this study have become available (Pacht *et al*. 2003). Patients receiving the experimental formula were reported to have lower concentrations of IL-8 in their alveolar fluid and a tendency to lower concentrations of LTB_4 and TNF-α. It is possible that the lower concentrations of LTB_4 and IL-8, both of which are potent leucocytes chemoattractants, may have been responsible for the lower neutrophil infiltration reported in the experimental group, and indeed an association was found between neutrophil counts and these concentrations. This study establishes that the experimental treatment decreases production of inflammatory mediators and infiltration of inflammatory leucocytes and that this outcome can result in marked clinical improvement in extremely-ill patients. As there are many differences in composition between the experimental and control formulas used it is not possible to ascribe the effects and benefits to any particular nutrient. However, the effects on LTB_4, IL-8 and TNF-α concentrations are consistent with the effects of long-chain *n*-3 PUFA reported elsewhere and so it is tempting to ascribe the observed effects to *n*-3 PUFA.

Conclusions

The response to surgery and to traumatic insults may involve excessive inflammation and an immunosuppressed state in some patients. *n*-6 PUFA may play a role in creating this state, and approaches to decrease the amount of linoleic acid used in parenteral lipid emulsions are being sought. One approach is to partly replace soyabean oil with fish oil in such emulsions. Long-chain *n*-3 PUFA from fish oil decrease the production of inflammatory eicosanoids and cytokines. They act both directly (by replacing arachidonic acid as an eicosanoid substrate and by inhibiting arachidonic acid metabolism) and indirectly (by altering the expression of inflammatory genes through effects on transcription factor activation). Thus, long-chain *n*-3 PUFA are potentially-useful anti-inflammatory agents and may be of benefit in patients at risk of developing a hyperinflammatory state and sepsis. An emerging application of *n*-3 PUFA is in patients undergoing surgery or in critically-ill patients; here they may be added to parenteral (or enteral) formulas. Parenteral nutrition that includes *n*-3 PUFA appears to preserve immune function better than standard formulas and to partly prevent some aspects of the inflammatory response. Studies to date are suggestive of clinical benefits from this approach, especially in patients who have undergone surgery, although evidence of clinical benefit in patients with sepsis is emerging.

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https://doi.org/10.1079/PNS2006500 Published online by Cambridge University Press

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