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‘Nutrition in the severely-injured patient’

The scientific basis of immunonutrition†

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Substrates with immune-modulating actions have been identified among both macro- and micronutrients. Currently, the modes of action of individual immune-modulating substrates, and their effects on clinical outcomes, are being examined. At present, some enteral formulas are available for the clinical setting which are enriched with selected immune-modulating nutrients. The purpose of the present paper is to review the scientific rationale of enteral immunonutrition. The major aspects considered are mucosal barrier structure and function, cellular defence function and local or systemic inflammatory response. It is notable that in critical illness the mucosal barrier and cellular defence are impaired and a reinforcement with enteral immunonutrition is desirable, while local or systemic inflammatory response should be down regulated by nutritional interventions. The results available from clinical trials are conflicting. Meta-analyses of recent trials show improvements such as reduced risk of infection, fewer days on a ventilator, and reduced length of intensive care unit and hospital stay. Thus, a grade A recommendation was proclaimed for the clinical use of enteral immune-modulating diets. Improvement in outcome was only seen when critical amounts of the immune-modulating formula were tolerated in patients classified as being malnourished. However, in other patients with severe sepsis, shock and organ failure, no benefit or even disadvantages from immunonutrition were reported. In such severe conditions we hypothesize that systemic inflammation might be undesirably intensified by arginine and unsaturated fatty acids, directly affecting cellular defence and inflammatory response. We therefore recommend that in patients suffering from systemic inflammatory response syndrome great caution should be exercised when immune-enhancing substrates are involved which may aggravate systemic inflammation.

Immunonutrition: Immune-modulating substrates: Enteral nutrition

The interrelationship between nutrition and the immune system has become the focus of ever increasing attention as an increasing number of substrates are being identified as having an immune-modulating function. Immunonutrients might be identified among macro- and micronutrients. Amino acids such as glutamine, arginine, cysteine and taurine, as well as nucleotides, are important immune-modulating substrates. Lipids that may be involved include monounsaturated and polyunsaturated fatty acids (PUFA), as well as short-chain fatty acids. Numerous substrates that interact with the immune system have been identified among vitamins and trace elements (vitamins A, C and E, Zn and Se). Based on experimental observation, many immunomodulatory effects have been claimed for a long time, but their clinical significance has only been recognized since the early 1980s. Indeed, the levels of inclusion of immune-modulating substrates clearly exceeds the amount used in a simple prevention of deficits. However, ‘pharmacological’ immunonutrition should simultaneously satisfy both the metabolic and immunological needs of the patient. The rationale for writing the present review is to examine the scientific basis of immunonutrition in the

Abbreviations: EPA, eicosapentaenoic acid; GSH, glutathione; IL, interleukin; LT, leukotriene; NOS, NO synthase; PUFA, polyunsaturated fatty acids; SIRS, systemic inflammatory response syndrome.

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Areas of immune defence and their modulation by defined substrates

In order to simplify this task, the immune defence system can be subdivided into three sites of action representing potential targets for specific nutritional substrates: (1) mucosal barrier function; (2) cellular defence function; (3) local or systemic inflammation (Fig. 1).

The mucosal barrier function of the intestinal mucosa represents the first line of defence against translocating pathogens, and it is already considered important in relation to early enteral nutrition of critically ill patients (Gardiner et al. 1995). Indeed, sufficient availability of suitable substrates is currently considered the major tool in maintaining the structure and functionality of the mucosal barrier.

Cellular defence function includes the specific and non-specific cellular immune response. Following invasion of pathogens it represents the second line of defence, consisting of granulocytes, macrophages, lymphocytes and plasma cells. The complex interactions between these effector cells are coordinated through the release of cytokines and other mediators. Nutritional substrates can modulate the cellular and humoral defence system via modified mediator formation or by interference with signal transduction.

Essential components of the inflammatory immune response are represented by the activation of cascade systems, such as the coagulatory or the complementary system. Moreover, mediators are involved which include cytokines, eicosanoids, platelet-activating factor and NO, as well as vasoactive amines and kinines. Systemic inflammatory response is manifest at the endothelium, the smooth vascular and bronchial muscles, and at platelet aggregation. This response may impair microcirculation, pulmonary gas exchange, vascular permeability, coagulation, as well as substrate utilization, and thus may influence organ function. Thus, a selective quantitative and qualitative choice of the supply of certain defined nutritional substrates which serve as the precursors of mediators may modulate the severity of the inflammatory immune response.

The actions of pathogens on the systemic immune response are illustrated in Fig. 2. Although a boost of cellular defence functions may initially take place; in the long term this boost is followed by the suppression of these functions, an effect described by the term 'immune paralysis'. Within the framework of these events experimental and clinical data lend credence to the idea of understanding defined substrates as 'pharmacologically effective agents' by which the cellular defence function can be restored or the systemic inflammatory response alleviated. Consequently, glutamine, arginine, nucleotides and PUFA are considered of primary relevance.

Glutamine

Glutamine is the most prevalent free amino acid in the human body. In skeletal muscle glutamine constitutes >60% of the total free amino acid pool (Bergström et al. 1974). It is a precursor that donates N for the synthesis of purines, pyrimidines, nucleotides, amino sugars and glutathione (GSH), and is the most important substrate for renal ammoniagenesis (regulation of the acid–base balance). Glutamine serves as a N transporter between various tissues, and represents the major metabolic fuel for the cells of the gastrointestinal tract (enterocytes, colonocytes; Windmueller, 1982; Souba, 1991) as well as for many rapidly proliferating cells, including those of the immune system (Calder, 1994). Consequently, the morphological and functional integrity of the intestinal mucosa appears to be protected by sufficient availability of glutamine. There is much evidence that hypercatabolic and hypermetabolic situations are accompanied by marked depressions in muscle intracellular glutamine. This response has been shown to occur after elective operations, major injury, burns, infections and pancreatitis, irrespective of nutritional attempts at the time of repletion. A reduction in the muscle free glutamine pool (approximately 50% of the normal level) thus appears to be a hallmark of the response to injury, infection and malnutrition (for references, see Fürst, 1994a). This response creates a glutamine-depleted environment, the consequences of which include enterocyte and immunocyte starvation (Bode & Souba, 1994). It has been suggested that glutamine becomes a conditionally essential amino acid during episodes of catabolic stress such as injury and sepsis.

Numerous experimental studies support this hypothesis. Glutamine-supplemented enteral or parenteral nutrition solutions are associated with increased intestinal mucosal thickness and DNA and protein content, reduced bacterial translocation after radiation (Souba, 1991), weakened adverse effects of experimentally induced enterocolitis (Rombeau, 1990), preserved intestinal mucosa during parenteral nutrition (Babst et al. 1993) and enhanced rat mucosal hyperplasia after small bowel resection (Klimberg et al. 1990). In vitro, glutamine has been shown to induce

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**Fig. 1.** Schematic representation of the three areas of immune defence affected by immunonutrients.
heat shock protein 70 and its RNA transcription in intestinal epithelial cells, thereby reducing cytolysis, induced by heat and oxidation (NH₃-CI; Wischmeyer et al. 1997; Chow & Zhang, 1998). Thus, glutamine supplementation reduced heat shock-induced cell death. This effect, together with the maintenance of cell growth, may play a key role in the prevention of intestinal mucosal atrophy.

In addition, glutamine supplementation has been reported to restore mucosal immunoglobulin A and enhance respiratory tract immunity (Li et al. 1997), prevent gut-derived sepsis in obstructive jaundice (Houdijk et al. 1997), reverse gut-derived sepsis due to prednisone administration (Gennari & Alexander, 1997) and enhance bacterial clearance in peritonitis (Furukawa et al. 1997).

Glutamine supplementation augments the cytotoxic activity of natural killer and lymphokine-activated killer cells (Alverdy, 1990; Babst et al. 1993; Horig et al. 1993) as well as adequate lymphocyte, killer cell and macrophage proliferation (Griffiths & Keast, 1990; Parry-Billings et al. 1990) and function (Griffiths & Keast, 1990; Wallace & Keast, 1992; Calder & Newsholme, 1992; Calder, 1994; Juretic et al. 1994). Leucocyte glutaminase activity is high, thus indicating a high rate of glutamine utilization (Calder, 1994). Recumbent immunocompetent cells already show a distinctive glutamine metabolism, that further increases by immunological provocation (Calder, 1994). All these effects emphasize that cellular defence function can be reinstalled by glutamine repletion in vitro and in vivo.

In experimental studies supplemental glutamine preserves hepatic and intestinal mucosal stores of GSH and maintains plasma concentrations (Hong et al. 1992; Harward et al. 1994; Denno et al. 1996; Yu et al. 1996). In the gut GSH is involved in the detoxification of reactive oxygen species and pro-oxidative nutrients. An experimentally induced intestinal GSH deficiency has been shown to be associated with impaired mucosal integrity and function (Martensson et al. 1990; Kelly, 1993). It has also been shown that lumen and lymphatic concentrations of lipid hydroperoxides were related to intestinal GSH status (Aw, 1997). Experimental feeding with glutamine results in a considerable increase in its gut fractional uptake and a marked increase in intestinal GSH fractional release, indicating increased intestinal GSH production (Cao et al. 1998). The biochemical explanation for these findings is based on the fact that the highly charged glutamic acid molecule, one of the direct precursors of GSH, is poorly transported across the cell membrane, whereas glutamine is readily taken up by the cell. Glutamine is then deaminated and thus can serve as a glutamic acid precursor (Hong et al. 1992). Obviously, glutamine-mediated GSH synthesis might be one of the most important factors in the systemic inflammatory response. It is proposed that tissue GSH synthesis is a crucial factor in causing the reversal of the clinical biochemical signs of critical illness.

Regarding the clinical application of glutamine, impressive confirmation that enteral glutamine therapy is effective in preventing infective complications has been reported recently in sixty patients with severe multiple trauma (Houdijk et al. 1998). In a randomized controlled study enteral glutamine nutrition at 25–30g/d (Houdijk, 1998) was commenced within 4h of trauma via a nasoduodenal tube for a minimum of 5 d. There was a significant reduction (−<−50 %) in the 15 d incidence of pneumonia, bacteraemia and severe sepsis. As a measure of the systemic inflammatory response, the group receiving glutamine showed lower levels of soluble tumour necrosis factor receptors. The strength of this study lies in the relatively homogeneous population of patients studied, and that it does

**Fig. 2.** Effects of invading pathogens on the systemic immune response and its modulation by substrates with immune-modulating action. PGE, prostaglandin E; LTB, leukotriene B; IL, interleukin; TNF, tumour necrosis factor.
not suffer the confounding factors present in multi-centre studies (Griffiths, 1999). However, the results of this fascinating study require confirmation. In a current study of a more heterogeneous group of intensive care unit patients able to tolerate enteral feeding (Jones et al., 1999), many of whom were already infected on admission, there was no suggestion of reduced mortality, but total post-intervention hospital costs were significantly reduced in both enteral and parenteral glutamine recipients.

In conclusion, the enteral route may be ideal when given early to the non-infected patient to improve gut-associated lymphoid tissue function and the immune defence against infection. For the already-severely-stressed or infected intensive care unit patient enteral supplements alone may be inadequate, and parallel parenteral support is likely to be required. It has been clearly demonstrated that during intensive care, the patient’s parenteral supplementation of enteral nutrition does not increase the risk to the patients and may even ensure a better overall outcome (Bauer et al., 1998).

Nucleotides

Nucleotides are important components for the synthesis of DNA, RNA and adenine nucleotides. Adequate nucleotide synthesis requires sufficient amounts of purines and pyrimidines. In healthy subjects they are efficiently absorbed from the diet which normally contains 1–2 g/d. Purines and pyrimidines are either derived from de novo synthesis or from RNA turnover by means of so-called ‘salvage pathways’. In the case of adequate protein intake, de novo synthesis is the main source of nucleotides; glutamine being the major N donor (Szondy & Newsholme, 1990). The role of nucleic acids is critical because expression of the synthesizing enzymes in the de novo pathway is apparently impaired during catabolic stress (Grimbly, 1994). During episodes of infection following injury and trauma the demand for nucleotides is increased in order to facilitate the synthetic capacity of the immune cells (Jyonouchi, 1994; Kulkarni et al., 1994). The absence of nucleotides (purines and pyrimidines) in the diet results in a selective loss of T-helper lymphocytes and a suppression of interleukin (IL) 2 production (VanBuren et al., 1994).

Parenteral solutions and the majority of enteral diets do not contain nucleotides. In clinical nutrition an adequate supply of nucleotides may be a critical factor in promoting intestinal function and immune status, as suggested by the findings of numerous experimental studies (Kulkarni et al., 1994; VanBuren et al., 1994; LeLeiko & Walsh, 1995; Cosgrove, 1998). In the experimental setting dietary nucleotide removal was associated with impaired mucosal integrity and function, which could be partly prevented or reversed by oral or intravenous supply of these substrates (LeLeiko et al., 1987; Nunez et al. 1990; Iijima et al., 1993). Decreased availability of nucleotides is associated with impaired T-cell function (VanBuren et al., 1983, 1990; Carver et al., 1990; Pizzini et al., 1990), weakened natural killer cell activity (Carver et al., 1990), delayed rejection of allogenic transplants (VanBuren et al. 1983), decreased mortality from graft v. host reactions (Kulkarni et al., 1984), suppressed lymphocyte proliferation (VanBuren et al. 1983; Kulkarni et al. 1989) as well as reduced IL-2 production (VanBuren et al. 1994). Moreover, reduced phagocytosis (Fanslow et al. 1988) and an impaired clearance of experimentally applied pathogens (Kulkarni et al. 1986) were induced by dietary removal of nucleotides. Most of these effects could be reversed by resumption of the dietary supply of nucleotides (Pizzini et al. 1990).

The question of whether the demand for nucleosides and nucleotides can exceed the endogenous synthetic capacity in human subjects remains to be answered, and implications with regard to impaired organ and system function are yet to be evaluated (Grimble, 1994). Notably, there is no relevant experimental or clinical evidence that nucleotides or nucleosides may enhance the systemic inflammatory response.

Arginine

Arginine is a dibasic amino acid which the body obtains from dietary sources and by endogenous synthesis via the urea cycle. During trauma and sepsis endogenous availability of arginine is reduced (Barbul et al., 1983; Kirk & Barbul, 1990; Nirgiotis et al. 1991). Arginine is metabolized within the enterocyte via the arginase pathway to ornithine and urea. Arginine, via the formation of glutamate, may yield increased amounts of proline and hydroxyproline, which are required for the synthesis of connective tissue. Moreover, arginine is the precursor of polyamine, histidine and nucleic acid synthesis. It is a promoter of thymic growth and an endocrinological secretagogue stimulating release of growth hormone, prolactin, insulin and anti-insulinemic hormones (Barbul, 1986). Most importantly, however, via the arginine deaminase pathway (Blachier et al., 1991), arginine has been shown to be the unique substrate for the production of the biological effector molecule NO. NO is formed by oxidation of one of the two identical terminal guanidino groups of L-arginine by the enzyme NO synthase (NOS). Of the three NOS isoenzymes characterized, two are constitutive, Ca2+-dependent (endothelial and neuronal) and generate lesser levels of NO than their inducible counterpart (Nathan & Xie, 1994). Inducible NOS is prominent in inflammatory conditions and it is also most often implicated as the producer of NO during the immune response. According to recent reports NO plays an essential role in the regulation of inflammation and immunity (Altman, 1996).

Inhibition of NO synthesis increased intestinal mucosal permeability in experimental models of ischaemia–reperfusion intestinal injury (Kubes, 1993) and acute necrotizing enterocolitis (Miller et al. 1993). In addition, administration of L-arginine reversed the effect of NOS inhibition (Kubes, 1993). These results suggest that basal NO production is important in minimizing the mucosal barrier dysfunction in these models. Arginine may also be of significance in the critically ill patient because of its potential role in immunomodulation (Kirk & Barbul, 1990; Evoy et al. 1998). It is hypothesized that arginine enhances the depressed immune response of individuals suffering from injury, surgical trauma, malnutrition or sepsis. In experimental animals as well as in human studies supplementation with arginine resulted in an
improved cellular response, a decrease in trauma-induced reduction in T-cell function and a higher phagocytosis rate (Kirk & Barbul, 1990).

It is notable that 5 years ago parenteral arginine was considered a novel and valuable tool to improve immunity and to beneficially influence metabolism and pathophysiology in cancer and trauma. Remarkably, in the current literature the intravenous arginine approach is almost absent, while emphasis is laid on enteral arginine nutrition. Presumably the prominent reports of the drawbacks and disadvantages of large amounts of parenteral arginine have been slowly recognized and considered (for references see Fürst & Stehle, 1995). In healthy human subjects and surgical and intensive care unit patients enteral arginine supplementation was accompanied by increased lymphocyte and monocyte proliferation as well as enhanced T-helper cell formation (Daly et al. 1988; Barbul, 1990; Cerra et al. 1990). Clinical studies have demonstrated moderate net N retention and enhanced protein synthesis compared with isonitrogenous diets in critically ill and injured patients. Following surgery for certain malignancies in elderly post-operative patients, supplemental arginine (25 g/d) enhanced T lymphocyte responses to phytohaemagglutinin and concanavalin A, and increased the CD4 phenotype number (Daly et al. 1988). Interestingly, insulin-like growth factor-1 levels were about 50 % higher, reflecting the growth hormone secretion induced by arginine supplementation. A high load of oral arginine (30 g/d) improved wound healing (Barbul et al. 1990) and enhanced blastogenic response to several mitogens (Sodeyama et al. 1993). Some of these studies were also associated with in vitro evidence of enhanced immunocactivity (Kirk & Barbul, 1990; Brittenden et al. 1994a,b; Beaumier et al. 1995). Thus, it is probable that the observed beneficial effects of these substrates were due to improved function of the immune system rather than improved gut barrier function.

Results available from clinical trials failed to demonstrate improvements in patient outcome (for references, see Lin et al. 1998). There is also some concern that arginine may enhance the systemic inflammatory response due to an enhanced NO release in patients with severe systemic inflammatory response syndrome (SIRS) or sepsis. This response would lead to a negative iono- and chronotropic response of the myocardium (Lowenstein et al. 1994), impaired coagulation (Radomski et al. 1990; deGraaf et al. 1992) and vascular dilatation leading to refractory hypotension (Lee et al. 1984; Lorente et al. 1993). Apparently, NO may exert cytotoxic effects as a non-specific effector inhibiting growth or killing off cells in an untargeted fashion (Lepoivre et al. 1991; Wink et al. 1991; Lowenstein et al. 1994). On the other hand, according to current knowledge, NO and NOS-mediated immunofactors as well as intracellular arginine are restricted to distinct compartments, thus supplemental arginine may not affect extracellular NO concentration (Moncada et al. 1991).

**n-3 Polyunsaturated fatty acids**

We are gradually understanding that lipids are more than sources of energy and building blocks for cell membranes, but may, in some circumstances, be considered as pharmacological agents provided through nutrition. This situation appears to be particularly true for the n-3 PUFA.

Fatty acids are characterized by the number of C atoms, the number of double bonds and the position of the first double bond, calculated from the methyl end of the molecule. Thus, 18:2n-6 represents linoleic acid which serves as the precursor for the formation of the most important fatty acids of the n-6 series such as arachidonic acid. 18:3n-3 represents α-linolenic acid, the parent compound of n-3 PUFA, with the first double bond being at C-3 from the methyl end. Whereas n-6 fatty acid deficiency has been recognized and considered, n-3 fatty acid deficiency is just now being appreciated. Delayed growth, neurobiological symptoms, skin lesions, reduced visual acuity, abnormal electroretinogram and reduced learning ability represent signs of n-3 fatty acid deficiency. Long-chain n-3 PUFA such as eicosapentaenoic (20:5n-3; EPA) and docosahexaenoic acid (22:6n-3) are built up in algae and plankton and the fish living on them, rendering deep-sea fish and fish oils produced from them the main dietary source of n-3 PUFA for human subjects.

With the enteral or parenteral intake of increased quantities of n-3 PUFA, the n-3:n-6 PUFA value in the phospholipid spectrum of the cell membrane in various tissues changes in favour of n-3 PUFA (Palombo et al. 1993; Morlion et al. 1996). Several laboratories have demonstrated that dietary pretreatment with n-3 PUFA favourably influences the pathophysiological response to endotoxins (Mascioli et al. 1988; Seidner et al. 1989) and exerts an important modulatory effect on eicosanoid and cytokine biology. The most likely way in which lipids might modulate pro-inflammatory cytokine biology is by changing the fatty acid composition in the cell membrane. As a consequence of the changes two interrelated phenomena may occur: (1) alteration in membrane fluidity; (2) alterations in products which arise from hydrolysis of membrane phospholipids (Grimble, 1998).

Changes in fluidity may alter the binding of cytokines and cytokine-inducing agonists to receptors (Stubbs & Smith, 1984; Murphy, 1990). For example, fluidity changes may alter G-protein activity, thereby changing adenylate kinase, phospholipase A2 and phospholipase C activity (for references, see Fürst & Kuhn, 2000).

Alterations in membrane phospholipids will also directly influence the synthesis of lipid-derived mediators such as the eicosanoids, phosphatidic acid, platelet-activating factor and the secondary messengers, diacylglycerol and ceramide (Grimble, 1992; 1998; Ross et al. 1999). By the action of the enzyme phospholipase A2, PUFA can be released from the membrane phospholipids and either act as a secondary messenger or alternatively serve as a precursor for the cyclo-oxygenase pathway (Kinsella et al. 1990). The latter pathway metabolizes arachidonic acid to the 2-series of prostaglandins, especially prostaglandins E2 and F2α and thromboxane A2. EPA is also an excellent substrate for the enzyme 5-lipoxygenase. The major advantages of EPA- and docosahexaenoic acid-derived metabolites can be summarized as follows: (1) EPA-derived thromboxane A2 is less active in platelet aggregation than thromboxane A2; (2) leukotriene (LT) B4 enhances chemotaxis, while other LT, e.g. LTC4, LTD4, and LTE4, augment vascular permeability...
and contractility. EPA is converted to LTB₅, which has only a small proportion of the activity of LTB₄ and platelet-activating factors, resulting in decreased chemotactic migration and endothelial cell adherence. This activity would mean that n-3 fatty acids exert major effects on the synthesis of LT by promoting an anti-inflammatory action; (3) feeding with fish oils is associated with profound changes in immunoregulatory processes, including the production and release of various cytokines, interleukines and interferons. It is currently assumed that, partly as a result of these changes, the natural history and progression of diseases with an inflammatory or immunological component may be altered; (4) consumption of EPA and docosahexaenoic acid reduces serum cholesterol, LDL and triacylglycerol concentrations (Fürst & Kuhn, 2000).

Indeed, inflammatory symptoms of rheumatoid arthritis, psoriasis, Crohn’s disease and ulcerative colitis are all ameliorated by fish-oil preparations, whether or not directly related to cytokine production. Consumption of EPA reduces the production of pro-inflammatory IL-1-α and -β and IL-6, as well as tumour necrosis factor-α and -β in response to an inflammatory stimulus (Endres et al. 1989, 1991; Caughey et al. 1996). The anti-inflammatory effects of fish oil may also include decreased production of inflammatory substances like LTB₄ and platelet-activating factors released by the action of cytokines, as well as a large reduction in cytokine-induced synthesis of prostaglandin E₂ and thromboxane B₂ in the colonic mucosa (Pomposelli et al. 1988; Endres et al. 1989; Fritsche & Cassity, 1992; Engstrom et al. 1996). These findings are in line with a decrease in arachidonic acid : EPA in blood mononuclear cell membranes as well as a decrease in neutrophil chemotaxis to LTB₄ (Lowry & Thompson, 1994). The combined observations may be partly explained by the finding that LTB₄ enhances blood monocyte IL-1 production after lipopolysaccharide exposure (Roła-Pleszcynski & Lemaire, 1985).

Fish oil supplementation suppresses autoimmune diseases and T-cell lymphocyte production of IL-2, and subsequent proliferation (Endres et al. 1993; Yaqoob & Calder, 1995). This mechanism involves down regulation of co-stimulatory molecules like leucocyte function-associated antigen, intracellular adhesion molecule-1 and CD₄ in T lymphocytes as well as co-stimulatory receptors and secretion of effector molecules from accessory cells (Calder, 1995; Harbighe, 1998). It should be remembered that in critically ill patients administration of n-3 PUFA is associated with a reduction in the 2-series of prostaglandins, thereby boosting the cellular defence function due to the ineffectiveness of feedback inhibition induced by prostaglandin E₂ (Lee et al. 1984; Ninnemann & Stockland, 1984; Terano et al. 1984; Lokes & Kinsella, 1987). This hypothesis is supported by experimental data showing that administration of n-3 PUFA during hypermetabolism is associated with increased cytokine production (Watanabe et al. 1991; Ertel et al. 1993), improved antigen presentation (Ertel et al. 1993), enhanced splenocyte proliferation (Ertel et al. 1993), improved opsonization indices (Alexander et al. 1986) and reduced mortality (Barton et al. 1991).

There are numerous studies showing suppression of T-cell-mediated immune function. This effect might be undesirable, especially in immune-suppressed individuals (Wu & Meydani, 1998). It could be demonstrated that the immunosuppression might be in part attributable to increased lipid peroxidation and decreased antioxidant (especially vitamin E) levels (Wu & Meydani, 1998). Recent studies have shown that the suppressive effect of n-3 fatty acid administration on T-cell function can be prevented by vitamin E supplementation (Meydani et al. 1991; Wu et al. 1996).

In conclusion, the potential clinical benefits of supplemental fish oil might be summarized as follows: reduced inflammatory response; anti-thrombotic effects; decreased reactivity to various stimuli (e.g. ventricular arrhythmias); maturation of the fetal central nervous system and retina DNA; maintenance of tissue microperfusion; increased tolerance to organ transplantation and improved function of the graft, as well as prevention of impaired cellular immunity when caused by increased prostaglandin E₂ production (Fürst & Kuhn, 2000). The latter concept, particularly, could gain considerable significance in hypermetabolism.

Clinical implication of immunonutrition: which patients benefit from immunonutrition?

Numerous clinical applications of immunonutrition have been reported (Moore, 1994; Bower et al. 1995; Senkal et al. 1995; Kudsk et al. 1996; Atkinson et al. 1998; Braga et al. 1998). At present, various enteral formulas are available containing substrates assumed to be beneficial, e.g. glutamine, arginine, nucleotides and n-3 fatty acids, as well as Se, vitamins E, C and A and β-carotene, at various concentrations (see Table 1). The clinical benefit of these immune-modulating diets on individual measures of cellular defence has been shown in post-operative or post-traumatic patients (Cerra, 1991; Daly et al. 1992; Moore, 1994; Kemen et al. 1995), yet the implication of expensive enteral preparations should be further justified. Indeed, it would be essential to demonstrate a reinforcement of cellular defence functions in association with an improvement in clinical outcome and morbidity. At present, there are numerous prospective randomized clinical studies with immune-modulating diets showing clear evidence for a reduced incidence of infectious complications, a reduced duration of ventilation, a shortened stay in the intensive care unit as well as in hospital, and reduced hospitalization costs (for references, see Zaloga, 1998). In an evaluation of a meta-analysis, two research groups, Beale et al. (1999) and Heys et al. (1999) demonstrated significant improvements in nearly all the outcome variables mentioned earlier.

Indeed, adequate measures for subjective clinical evaluation are a prerequisite for the classification of the manifold immunological settings. There are patients who are characterized as immune-suppressed, infection-threatened but not yet suffering from fulminant systemic infection. These patients include, post-operative tumour patients after chemotherapy and radiotherapy, surgical patients with wound infections or massive transfusion, as well as those with multiple trauma or burns; these patients include perfect candidates for immunonutrition. Patients already suffering from a severe form of SIRS or sepsis may...
require attention when selecting suitable immunonutrients. Substrates possessing anti-inflammatory properties might be of particular value, whereas the use of pro-inflammatory substrates, such as arginine, must be avoided.

Shortcomings and pitfalls with immunonutrition

Several of the recent clinical studies have been poorly designed. Much of the criticism relates to the characterization of patients. Frequently the control diets were not isonitrogenous and/or isenergetic. Many studies failed to establish the critical lower limit of tolerance relating to the volume of enteral nutritional preparations. This factor is of utmost importance, since immunomodulation is only beneficial in patients receiving the critical minimum amount of the enteral preparation. Furthermore, the study groups were often not stratified with regard to the severity of illness or to the expected outcome, resulting in difficulties in analysing subgroups. Similarly, different studies used different preparations with an inconsistent proportion of the individual immune-modulating substrates. The major question might be whether benefits of immunonutrition in patients suffering from shock, sepsis, and organ failure are equal to those in moderately-traumatized surgical patients. In this context it should be noted that existing meta-analyses did not show any improvements in the former group of patients, but rather demonstrated a tendency towards poorer outcome (Beale et al. 1999; Heys et al. 1999). In particular, the multi-centre study by Bower et al. (1995) showed an alarming tendency towards increased mortality in the most-severely-ill patients with immunonutrition. In addition, higher mortality, longer hospitalization, longer ventilation periods and increased treatment costs were seen in a subgroup of burn patients receiving the immune-enhancing formula (Saffle et al. 1997). Similarly, increased intensive care unit and hospital stay, increased ventilator time and increased incidence of pulmonary organ failure were reported with immune-enhancing diets (Mendez et al. 1996, 1997). These results might be a serious warning to the unrestricted use of immune-enhancing formulas in the most-seriously-ill patients. It should be emphasized that substrates intended to stimulate the cellular defence function would not simultaneously induce enhancement of systemic inflammation if used in patients with severe indication of critical illness.

Concluding remarks

Currently-available enteral nutrition preparations with an immune-modulating effect are first-generation products, their design being based on a ‘multi-pragmatic’ approach. The modulating effect of selected substrates on immune response is considered as pharmacological nutrition and is experimentally and clinically established. Pharmacological nutrition is a novel concept which has introduced a new dimension into the fascinating field of modern clinical nutrition (Fürst, 1998). It is proposed that as a result of this new approach it will be possible to improve immune function (Bower, 1990; Chandra, 1991), reduce the frequency of inflammation (Burton, 1994; Fürst, 1994b), improve gut barrier function (Sobza et al. 1990; Burton, 1994; Fürst, 1994b) and regulate cellular hydration state (Häussinger et al. 1993). The rapid increase in new information relating to this exciting approach is certainly only a prelude to its use in routine clinical settings.

Special caution should be exercised when dealing with patients with most severe appearances of SIRS, sepsis and organ failure. We put forward the hypothesis that certain immune-enhancing substrates like arginine and n-3 fatty acids may be responsible for an undesirable outcome, as they may aggravate ongoing systemic inflammation (Gonce et al. 1990; Heyland et al. 1994). In contrast, in experimental and clinical settings no adverse effects have been reported for glutamine and nucleotides. Thus, immune-modulating interventions which include arginine and n-3 PUFA should be undertaken with care if administered in complex immune-pathological situations such as severe SIRS or organ failure. Moreover, the absence of clinically-available immunological monitoring, the lack of profound patho-physiological understanding, as well as the lack of objectives for influencing immune responses in patients with fulminating systemic inflammation should prompt further efforts in basic and applied clinical research.

### Table 1. Composition (g/l) of available immune-modulating diets

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<th>Diet</th>
<th>Reconvan*</th>
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</tr>
<tr>
<td>Se</td>
<td>50</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>+</td>
</tr>
<tr>
<td>Vitamin A (mg/l)</td>
<td>0-7</td>
<td>1</td>
<td>0-8</td>
<td>47</td>
<td>+</td>
</tr>
<tr>
<td>β-Carotene (mg/l)</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vitamin E (mg/l)</td>
<td>10</td>
<td>30</td>
<td>336</td>
<td>215</td>
<td>+</td>
</tr>
<tr>
<td>Vitamin C (mg/l)</td>
<td>60</td>
<td>67</td>
<td>60</td>
<td>120</td>
<td>+</td>
</tr>
</tbody>
</table>

* Levels not stated.
† Novartis, Minneapolis, MN, USA.
‡ McGaw, Irvine, CA, USA.
§ Shriners Burn Institute, Cincinnati, OH, USA.
Il Ross Laboratories, Columbus, OH, USA.
References


Kinsella JE, Lokesh B, Broughton S & Whelan J (1990) Dietary polysaturated fatty acids and eicosanoids: potential effects on

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