

## The value of peri-operative nutrition in the sick patient

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It is now 60 years since Hiram Studley (1936) demonstrated the importance of weight loss in patients who were undergoing surgery. He studied forty-six patients with chronic peptic ulcer disease and examined the role of age of the patient, the type of surgery, the presence of pyloric stenosis, the duration of surgery and the surgeon, as possible prognostic indicators. None of these factors was shown to be important in predicting the patients outcome following surgery. However, it was observed that the amount of weight lost pre-operatively did predict post-operative outcome. Although seven of the forty-six patients died in the post-operative period, six of these patients had lost more than 20 % of their body weight. In contrast, only one patient who had lost less than 20 % of their body weight died.

More recent studies have shown that malnutrition is still a problem in 40 % of hospitalized patients. Furthermore, in patients who are undergoing gastrointestinal surgery, up to 30 % can be classified as having 'moderate' malnutrition (Detsky *et al.* 1987). This weight loss is associated with alterations in protein and fat metabolism, cellular function, modulation of intracellular enzyme activities, and defects in function of the immune system, skeletal muscle and respiratory function, and wound healing (Hill, 1992). It is not surprising, therefore, that weight loss is associated with an increased post-operative mortality and morbidity in patients undergoing surgery (Meguid *et al.* 1990). Nutritional support has been given to patients undergoing surgery, therefore, with the aim of reversing weight loss, improving nutritional status and reducing the risks of post-operative morbidity and mortality.

The present paper will review the role of nutritional support given to patients in the peri-operative period by the parenteral and enteral routes. In addition, the role of specific nutrients and their use in such patients will also be examined.

### PARENTERAL NUTRITION IN THE PERI-OPERATIVE PERIOD

The role of total parenteral nutrition (TPN) in the peri-operative period in preventing post-operative complications and in reducing post-operative mortality has been investigated in prospective randomized controlled studies (Table 1). These studies have frequently involved small numbers of patients, have employed different nutritional regimens (both in duration of pre- and post-operative feeding and different energy and protein intakes), and have often evaluated different study end-points, e.g. effects on biochemical indices of nutritional status (e.g. serum protein levels, N balance studies), anthropometric markers of nutritional status (e.g. body composition, skinfold thickness), or on clinical variables (e.g. complications, infective episodes and mortality).

The first randomized trial designed to evaluate the role of peri-operative parenteral nutritional support was reported by Holter & Fischer (1977). They evaluated fifty-six patients with cancers of the gastrointestinal tract who had lost weight and were to undergo surgical resection of the tumours. The patients received either TPN (80 g protein with 8.3 MJ/d) for 3 d before surgery and for 10 d post-surgery or not to receive any nutritional support. The findings from this study demonstrated that the group of patients receiving

Table 1. *Effects of total parenteral nutritional (TPN) support in the peri-operative period*

	Patient group	No. of patients	Protocol	Results
Heatley <i>et al.</i> (1979)	Gastrointestinal cancers	75	Randomized to receive TPN and oral diet, or oral diet alone for 7–10 d before surgery	Patients in the TPN group had fewer wound infections than patients taking the oral diet alone. This effect was more marked in patients with albumin < 35 g/l
Muller <i>et al.</i> (1982)	Gastrointestinal cancers	125	Randomized to either TPN, or a standard oral diet for 10 d before operation	TPN group had a reduced mortality (3% v. 11%) and a reduced morbidity when compared with patients taking standard oral diet.
Veterans Affairs Total Parenteral Nutrition Co-operative Study Group (1991)	Thoracotomy or laparotomy	395	Randomized to receive TPN for 7–15 d before surgery and 3 d after surgery, or to have a standard oral diet	No differences in mortality or morbidity between the two groups of patients. Overall, increased risk of septic complications in patients receiving TPN. However, reduced risk of complications (approximately 50% reduction) in patients classified as 'severely' malnourished
Mullen <i>et al.</i> (1980)	Intra-abdominal cancers	145	Randomized to receive TPN for 10 d before surgery, or a standard oral diet	TPN group had reduction in incidence of major complications, but no differences in mortality when compared with the group taking the oral diet
Fan <i>et al.</i> (1994)	Hepatocellular carcinoma	125	Randomized to received TPN for 7 d before and 7 d after hepatic resection, or an oral diet	TPN group had reduced post-operative morbidity compared with oral group (34% v. 55%); benefit most marked in patients with cirrhosis or those undergoing major resections

TPN had a reduction in the incidence of major complications of approximately 30 %, although this did not achieve statistical significance. A clinical benefit of TPN in the peri-operative period was first reported by Moghissi *et al.* (1977). Patients with carcinoma of the oesophagus were randomized to receive either TPN given for 5–7 d before surgery and then for 6–7 d post-operatively, or to receive intravenous crystalloids and no nutritional support. The benefits noted in the TPN group of patients were an improved N balance (positive in the TPN patients but negative in the group receiving intravenous fluids) and better wound healing.

A larger study was subsequently reported by Heatley *et al.* (1979) which also suggested a beneficial effect of TPN given to patients in the peri-operative period. A total of seventy-five patients with upper gastrointestinal cancers received either a standard hospital diet (12.5 MJ and 15 g N/d) or the standard hospital diet supplemented with TPN (167 kJ/d). These nutritional regimens were given for 10 d pre-operatively. The patients receiving the TPN supplementation were observed to have fewer wound infections than those receiving the standard oral diet only. Furthermore, this reduction in wound infections only occurred in patients who had a serum albumin concentration of less than 35 g/l before entering the study.

A beneficial effect of the provision of TPN in the peri-operative period was demonstrated by Muller *et al.* (1982). This was a relatively large study of 125 patients who had intra-abdominal cancers of various types. Patients were randomized to receive either TPN (1.5 g amino acids/kg per d and 11 g glucose/kg per d), given for 10 d before surgery, or a standard hospital diet (10.0 MJ/d). Two main beneficial effects of TPN were observed; there was a significant reduction in the risks of post-operative complications (anastomotic leak, peritonitis, intra-abdominal abscesses, ileus) and also the post-operative mortality was reduced by threefold in patients receiving TPN. Clinical benefit with supplemental nutrition has not been a consistent finding and other studies have failed to show significant benefit from nutritional support. However, other beneficial effects such as improvements in serum proteins, N balance, nutritional status, reduction in the duration of hospital stay have been reported.

A larger study evaluating the effect of TPN in the peri-operative period was reported recently by the Veterans Affairs Total Parenteral Nutrition Co-operative Study Group (1991). This study was a multi-institutional, prospective, randomized controlled trial which had been designed in an attempt to provide a definitive answer to the question of the benefits of nutritional support in the peri-operative period. The patients included in this study were undergoing elective laparotomy or thoracotomy, with approximately two-thirds of patients having malignant disease. A total of 3259 patients were considered for the study, but after a variety of exclusions (e.g. not expected to survive for 90 d, had TPN within the last 15 d or undergone other surgical procedures within the previous month), 395 patients were studied. These patients were all classified as being 'malnourished' (according to a nutrition risk index,  $(1.519 \times \text{serum albumin (g/l)} + 0.417 \times (\text{current weight/usual weight}) \times 100$ ; a value of less than 83.5 defined those who were severely malnourished), or a combination of weight loss, a reduced serum albumin and/or reduced serum prealbumin). Patients were randomized to receive either TPN (4.2 MJ above resting energy expenditure and energy : N 150 : 1) or a control diet (standard hospital diet pre-operatively, fluids for the first 72 h post-surgery and oral feeding thereafter as clinically indicated). The patients were followed up for 90 d following surgery.

The primary end-points of this study were the incidence of major post-operative complications, with secondary end-points being mortality, all complications, infectious complications, non-infectious complications, and major complications after stratification

for the patient's underlying degree of malnutrition. The results of this study revealed that the incidence of major complications was similar for the TPN and control groups of patients. There was, however, a higher rate of infectious complications in the TPN group, when compared with the control group (14% *v.* 6%). In addition, there was a small increase in the incidence of non-infectious complications in the control group (17% *v.* 22%), but this did not achieve statistical significance. However, it was noted that this increase was mainly in those patients who were categorized as either 'borderline' or 'mildly' malnourished. A subgroup analysis of complications encountered by the patients according to their nutritional state demonstrated an important finding. The 'severely'-malnourished group of patients (comprising a total of only fifty patients) experienced fewer non-infectious complications than did the control patients (5% *v.* 43%), but there was no difference in infectious complications. However, it should be noted that only fifty patients fell into the severely malnourished category. This study again confirmed that TPN was of limited benefit in minimally-malnourished patients, although the severely-malnourished patients (less than 5% of the study population) may benefit from pre-operative TPN.

Fan *et al.* (1994) have also reported beneficial effects of peri-operative TPN in certain patients with primary liver cancer who were undergoing surgical resection. In this study, patients were randomized to receive either peri-operative TPN for 7 d before and 7 d after, surgery or alternatively to receive oral intake before surgery and intravenous fluids and electrolytes following surgery. Patients in the TPN group had less post-operative morbidity (34% *v.* 55%) and fewer infectious complications (17% *v.* 37%), than patients in the control group. The patients who benefited most from TPN were those with cirrhosis. In this subgroup of patients with cirrhosis, TPN supplementation resulted in a lowering of the post-operative morbidity by almost 50%. Furthermore, patients undergoing a 'major' hepatectomy also benefited, with a significant reduction in post-operative morbidity.

#### ENTERAL NUTRITION

The enteral route of nutrient administration has also been used in the provision of nutrition to patients in the peri-operative period. Although there are many advantages associated with the provision of nutrients by the enteral route, recent interest has focused on the barrier function of the gut. Under normal circumstances the gut prevents the entry of bacteria and endotoxin into the systemic circulation, hence preventing their widespread dissemination. The maintenance of this normal gut barrier function requires the interaction of several factors, e.g. the resident intestinal microflora, normal gut motility, normal intestinal epithelial structure and function, hormones and the provision of intraluminal nutrients.

Experimental studies in animals receiving TPN for short periods have shown that this can result in mucosal atrophy (Mainous *et al.* 1991) and bacterial translocation (Li *et al.* 1989). Moreover, these changes can be reversed by the provision of enteral nutrition. Studies in patients receiving TPN have also demonstrated changes in the gut wall. For example, TPN has resulted in significant decreases in mucosal thickness and reduced heights of both the villi and microvilli (Guedon *et al.* 1986; van der Hulst *et al.* 1993), decreased intestinal mucosal brush-border enzyme activity (Guedon *et al.* 1986), and an increased intestinal permeability to lactulose (van der Hulst *et al.* 1993). The importance of this impairment in intestinal barrier function is that there is an increased incidence of infective complications in patients (Sedman *et al.* 1994).

*Studies evaluating enteral nutrition in the peri-operative period*

Studies have also evaluated the role of enteral nutrition, given in the peri-operative period, to patients undergoing surgery. A variety of feeding regimens have been employed and the majority of these studies have provided the nutritional support following surgery. However, there have been two reports of the use of enteral nutritional support given before surgical intervention (Shukla *et al.* 1984; Meijerink *et al.* 1992; Table 2).

In the first of these studies (Shukla *et al.* 1984), 110 malnourished patients were randomized to receive enteral hyperalimentation (14.6–16.7 MJ/d) for 10 d or a standard diet. It was found that patients receiving enteral hyperalimentation had an improved nutritional status (serum albumin and anthropometric indices), enhanced immune function (cellular and humoral immunity) and a better N balance than patients eating a standard diet. In addition, there were also clinical benefits in the supplemented group of patients that were observed in the post-operative period. These latter patients had a reduced risk of wound infection (11 % *v.* 37 %), a reduced hospital stay (10 d *v.* 13 d) and a lower mortality (6 % *v.* 12 %), when compared with the non-supplemented group of patients. In the second of these studies, Meijerink *et al.* (1992) evaluated 151 patients with gastric or colorectal cancer in the pre-operative period. The aim of their study was to determine what effect nutritional supplementation, given through the enteral route (for 10 d), had on post-operative morbidity and mortality. Patients were stratified according to weight loss (less than or greater than 15 %), age less than, or greater than 65 years, and gastric or colo-rectal tumours. They received either enteral nutritional support (150% of basal energy expenditure), or no supplementation. The patients not receiving supplementation were split into two groups: those who were not nutritionally depleted and those who were nutritionally depleted. The results from this study revealed that there were no differences in the incidences of septic complications between the patients in the nutritional-support group and the non-nutritionally-depleted control patients. However, in patients who had lost more than 10 % of their body weight, and who had over 500 ml blood loss during surgery, there was a significant decrease in major complications as a result of nutritional support.

The role of post-operative nutritional support in patients undergoing surgery for fractured necks of femur also has been investigated, with beneficial effects being reported. Bastow *et al.* (1983) evaluated 744 elderly women with fractured necks of femur and divided them into three groups on the basis of anthropometric measurements (arm thickness and triceps skinfold thickness). Patients were categorized as being either 'well-nourished', 'thin' or 'very thin'. They studied 122 of these patients from the 'thin' and 'very thin' groups, in the post-operative period. The patients were randomized to a supplementary feeding regimen (4.2 MJ and 28 g protein) given overnight, or to receive no nutritional supplementation. This feeding regimen was continued until the patients were discharged from hospital, or until they could not tolerate the nasogastric feeding tube. The supplemental feeding was well tolerated by about 80 % of the patients in this group. It was documented that the supplemented group of patients had improvements in their nutritional status, as assessed by anthropometry and plasma proteins. In addition, these patients also had a shorter rehabilitation time and a reduced hospital stay when compared with patients not receiving nutritional supplementation. It was also observed that these effects were most marked in patients who were categorized as being 'very thin'. The mortality in these patients was also less than that in the non-supplemented patients (8 % *v.* 22 %), but this did not achieve statistical significance.

Delmi *et al.* (1990) subsequently reported their study of nutritional support in fifty-nine elderly patients with femoral neck fractures. In this study, the patients received either a nutritional supplement (20 g protein and 1.1 MJ/d) or no nutritional supplementation. The supplementation began as soon as the patient entered the orthopaedic unit and was

Table 2. Effects of enteral nutritional support in the peri-operative period

Patient group	No. of patients	Protocol	Results
Sagar <i>et al.</i> (1979)	30	Randomized to enteral diet, or intravenous fluids only, for 7 d after surgery	Patients receiving supplementation had improved N balance, lost less weight and had a shorter hospital stay, compared with control patients
Shukla <i>et al.</i> (1984)	110	Randomized to receive either enteral hyperalimentation, or a standard diet for 10 d before surgery	Patients receiving enteral hyperalimentation had an enhanced immune response (cellular, humoral), reduced loss of N, reduced morbidity and mortality
Bastow <i>et al.</i> (1983)	122	Randomized to receive enteral hyperalimentation, or hospital diet for up to 28 d after surgery	Patients receiving supplementation had improved weight gain and shorter rehabilitation time than non-supplemented patients
Delmi <i>et al.</i> (1990)	59	Randomized to receive enteral hyperalimentation, or a standard diet (mean duration was 32 d)	Patients in supplemented group had shorter hospital stay, reduced morbidity and mortality, compared with non-supplemented patients
Meijerink <i>et al.</i> (1992)	100	Randomized to receive either enteral nutrition for 10 d before surgery, or to proceed straight to surgery	No differences in morbidity and mortality between the two groups of patients
Carr <i>et al.</i> (1996)	28	Patients received either enteral feeding, or intravenous fluids after laparotomy	Patients receiving enteral nutrition had reduced incidence of complications

continued into the rehabilitation period. It was found that the rates of complications and deaths were significantly lower in the patients receiving nutritional supplementation. Furthermore, the supplemented patients had a reduction in complications and a lower mortality when assessed 6 months after the fracture. These authors also reported that nutritional supplementation resulted in a shorter hospital stay.

A recent study has also reported the beneficial effects of post-operative enteral nutrition in patients who have undergone major abdominal surgery (Carr *et al.* 1996). Thirty patients undergoing laparotomy for gastrointestinal resections were randomized to receive either immediate post-operative enteral feeding (approximately 6.9 MJ and 60 g protein) through a nasojejunal tube, or to have standard intravenous crystalloids, until the resumption of normal oral feeding. In this study, enteral nutrition resulted in an improved N balance and a significant decrease in gut permeability when compared with patients receiving intravenous fluids only. In addition, there was a significant reduction in post-operative complications in the group of patients receiving enteral nutrition.

Not all studies have demonstrated clinical benefits of enteral nutritional support (Hoover *et al.* 1980; Smith *et al.* 1985; Frankel & Horowitz, 1989; Schroeder *et al.* 1991). However, other beneficial effects in terms of weight gain, N balance and recovery time have been reported (Sagar *et al.* 1979; Ryan *et al.* 1981; Bastow *et al.* 1983; Shukla *et al.* 1984; Smith *et al.* 1985).

#### *Enteral or parenteral route of nutrient administration?*

Few trials have compared the efficacy of enteral *v.* parenteral nutrition in surgical patients in the peri-operative period. Moore *et al.* (1992) published a meta-analysis of eight randomized trials (two published and six unpublished) which had addressed this question in patients who had undergone a variety of surgical procedures. A total of 240 patients were analysed, 118 receiving enteral nutrition, and 112 receiving parenteral nutrition. This analysis revealed that there was a significant reduction in the number in the enteral nutrition group who experienced infective complications, when compared with patients receiving TPN (18% *v.* 35%). Further subgroup analyses were undertaken which demonstrated that it was the patients who had experienced trauma, in particular blunt trauma, who had the most significant reduction in infective complications when given enteral nutrition rather than TPN. However, these studies have been criticized because of methodological problems in the non-published trials.

In patients with acute pancreatitis, enteral nutrition also appears to have benefits over TPN. In a small randomized trial in twenty-three patients, Windsor *et al.* (1996) found that enteral nutritional support resulted in a decrease in the acute-phase response and reduced the incidence of the systemic inflammatory response syndrome, when compared with patients receiving TPN. However, not all studies have demonstrated benefits of enteral nutritional support. von Meyenfeldt *et al.* (1992) were unable to show any difference in septic complications, morbidity and mortality, in 101 patients who were randomized to receive either enteral nutrition or TPN for 10 d before surgery.

### TARGETED NUTRITION

#### *L-Arginine*

L-Arginine is considered to be a non-essential amino acid which becomes essential under stressful circumstances, e.g. sepsis and trauma (Kirk & Barbul, 1990). L-Arginine is required as a substrate for the synthesis of proteins, creatine, polyamines and NO (for

review, see Brittenden *et al.* 1994a; Heys *et al.* 1996). However, when administered orally in large quantities (in animal experimental studies) it has important effects on immune function, N metabolism and wound healing (Brittenden *et al.* 1994a).

In studies in man it has been shown that dietary supplementation with L-arginine (25 g/d) for 14 d resulted in an enhanced wound healing, as assessed by an increased synthesis of hydroxyproline (Barbul *et al.* 1977). Also, beneficial effects on N metabolism have been reported. Patients undergoing surgery for both benign and malignant disease have a reduced loss of N in the post-operative period if they receive dietary supplementation with L-arginine (Elsair *et al.* 1978; Daly *et al.* 1988).

The beneficial effects of L-arginine on the immune system have been shown in healthy volunteers and in patients with either benign or malignant diseases. Park *et al.* (1991) investigated the effects of adding L-arginine to the culture medium containing the lymphocytes taken from healthy volunteers. They found that this resulted in an enhanced response to mitogenic stimulation. Other studies in both healthy volunteers and patients with malignant disease have demonstrated that supplementing the diet with L-arginine results in enhanced responses to mitogens, increased natural killer (NK) and lymphokine-activated killer cell activities, and increased numbers of circulating T helper cells (Table 3).

#### *L-Glutamine*

Glutamine is the most abundant amino acid in the body, making up more than half the free intracellular amino acid pool (Bergstrom *et al.* 1974). It is a non-essential amino acid and its roles include: the transport of N between tissues, a precursor for the manufacture of purines and pyrimidines, and a fuel for a variety of cells in the body, in particular colonocytes and enterocytes. In certain circumstances, e.g. stress, sepsis and trauma, the plasma and intracellular concentrations of glutamine decrease and these decreases have been shown to correlate with patient survival (Roth *et al.* 1982).

Glutamine supplementation has beneficial effects on N metabolism in patients undergoing surgery. For example, in patients undergoing cholecystectomy, glutamine supplementation given in the post-operative period resulted in a substantial reduction in whole-body N loss, when compared with patients not receiving glutamine supplementation. Furthermore, the decrease in the intracellular glutamine concentration that occurred post-operatively was smaller (Hammarqvist *et al.* 1989). Similarly glutamine supplementation given to patients undergoing surgery for intra-abdominal malignant disease also reduced daily negative N balance and increased the levels of L-glutamine in skeletal muscle, when compared with non-supplemented patients.

Beneficial effects of glutamine on the immune system have been shown by O'Riordain *et al.* (1994). These authors studied patients with colo-rectal cancer undergoing surgical removal of the tumour. Patients received TPN, but with or without glutamine supplementation, for 6 d post-operatively. This study revealed that glutamine supplementation produced an increase in T cell lymphocyte DNA synthesis in response to mitogenic stimulation. However, there were no differences in interleukin (IL)-2, IL-6 or tumour necrosis factor (TNF) production by isolated peripheral blood mononuclear cells.

The clinical benefit of glutamine supplementation was confirmed in patients undergoing bone-marrow transplantation (Ziegler *et al.* 1992). After the patients had undergone transplantation, they were randomized to receive either glutamine supplementation (approximately seven times the normal daily intake) or no glutamine supplementation for 4 weeks. The results of this study revealed that not only did glutamine-supplemented patients have better improved N balances, but they also had fewer infections and shorter



Table 3. The effects of L-arginine supplementation on host defences (From Heys *et al.* 1996; with permission)

	Patient group	No. of patients	Protocol	Outcome
Daly <i>et al.</i> (1988)	Gastrointestinal malignancies	30	Patients received enteral nutrition and randomized to either 25 g L-arginine or 43 g glycine/d for 7 d after surgery	Increased <i>in vitro</i> response of lymphocytes to mitogens on the first post-operative day and increased CD4 + lymphocytes. No difference in clinical outcome or infectious complications
Barbul <i>et al.</i> (1990)	Healthy volunteers	36	Standard diet and randomized to receive either L-arginine (25 g/d or 17 g/d) or no supplementation	Increased <i>in vitro</i> responses of lymphocytes to mitogens with L-arginine supplementation after 7 d
Barbul <i>et al.</i> (1981)	Healthy volunteers	27	Twenty-one volunteers received L-arginine (30 g/d) for 7 d; six volunteers received L-arginine (30 g/d) for 3 d	L-Arginine supplementation resulted in enhanced <i>in vitro</i> responsiveness of peripheral blood lymphocytes to mitogens; effects present after 3 d but more marked by day 7
Park <i>et al.</i> (1991)	Healthy volunteers	13	Standard diet supplemented with L-arginine (30 g/d) for 3 d	NK and LAK cell cytotoxicity increased by 91% and 58% respectively; circulating CD56 + (LAK) cell numbers increased following L-arginine supplementation
Brittenden <i>et al.</i> (1994a)	Locally-advanced breast cancer	24	Standard diet supplemented with L-arginine (30 g/d) for 3 d	Lymphocyte responses to mitogens, NK and LAK cell cytotoxic activities all increased but no change in CD16 + (NK) or CD56 + (LAK) cell numbers after L-arginine supplementation
Brittenden <i>et al.</i> (1994b)	Locally-advanced breast cancer	16	Standard diet supplemented with L-arginine (30 g/d) before chemotherapy on six occasions	Stimulation of NK and LAK cell cytotoxicity by L-arginine supplementation on each of the six occasions

NK, natural killer; LAK, lymphokine-activated killer; CD, cluster of differentiation antigens.

hospital stays, when compared with non-supplemented patients. However, this was a small study and further larger studies are required to confirm these clinical benefits.

### *Essential fatty acids (EFA)*

EFA (*n*-3 and *n*-6) play important roles in cellular metabolism. They are important components of cell membranes and are precursors for the synthesis of a variety of substances which can regulate various aspects of metabolism and immune function, e.g. leukotrienes, prostaglandins (PG) and platelet-aggregating factors (Kinsella & Lokesh, 1990). In particular, the potent immunosuppressor, PGE<sub>2</sub> is derived from the metabolism of *n*-6 EFA. In contrast, the metabolism of *n*-3 EFA leads to the production of PGE<sub>3</sub>, which is a less-potent suppressor of the immune system than is PGE<sub>2</sub> (Alexander *et al.* 1986). Furthermore, there is an increased production of PGE<sub>2</sub> following traumatic injury.

This finding has prompted studies evaluating the use of *n*-3 EFA as possible enhancers of the depressed immune response that occurs in sepsis. However, the studies in animal models have revealed conflicting results; beneficial effects on survival have been reported (Mascioli *et al.* 1989; Barton *et al.* 1991), while other reports indicate that *n*-3 EFA supplementation results in either no difference in survival or worse survival (Alexander *et al.* 1986; Clouva-Molyvdas *et al.* 1992).

Studies in man, however, have indicated that dietary supplementation with *n*-3 EFA results in suppression in various aspects of the immune system in healthy volunteers (Meydani *et al.* 1991). Studies in patients with colo-rectal cancer have demonstrated also that supplementation with a mixture of *n*-3 and *n*-6 EFA will result in a suppression of the response of peripheral blood lymphocytes to mitogens, reduction in natural cytotoxicity and decreased levels of a range of circulating cytokines (Purasiri *et al.* 1994*a,b*, 1995). Similarly, in patients with inflammatory bowel disease, dietary supplementation with *n*-3 EFA (eicosapentaenoic acid and docosahexaenoic acid) resulted in suppression of NK cell activity (Almallah *et al.* 1996).

### *Nucleotides*

Nucleotides are necessary for the synthesis of RNA and DNA, proteins, carbohydrates and lipids. Initial studies in animal experimental models demonstrated that the loss of antibody-producing function in irradiated animals could be restored by giving the animals nucleic acid-rich material. Subsequently, synthetic polyribonucleotides were developed and shown to have a range of immunomodulatory effects in animal studies (Khan *et al.* 1995*a*). For example, polyribonucleotides resulted in a stimulation of the number and function of circulating T lymphocytes, increased activity of T suppressor cells and stimulated natural cytotoxicity (Donner *et al.* 1977; Morris & Johnson, 1978; Youn *et al.* 1987). Furthermore, in an animal model of sepsis, polyribonucleotide administration resulted in improved survival in mice (Adeji *et al.* 1993). In human studies, the intravenous administration of a synthetic polyribonucleotide, polyadelylic polyuridylic acid (PAPU) stimulated macrophage function and induced the release of IL-1 $\beta$ , IL-2, IL-6, TNF $\alpha$  and interferon- $\gamma$  (Khan *et al.* 1995*b*; Dy *et al.* 1991).

### *Clinical studies evaluating combinations of specific nutrients*

Initial trials of combinations of L-arginine, *n*-3 fatty acids and polyribonucleotides have been reported in a variety of patients, including patients undergoing surgery. The effects of

Table 4. *Trials of nutrient combinations in clinical practice (Adapted from Heys et al. 1996; with permission)*

	Patient group	No. of patients	Protocol	Outcome
Daly <i>et al.</i> (1992)	Oesophageal, gastric, pancreatic cancers	85	Randomized to receive enteral diet (Osmolite HN®; Ross Laboratories, Columbus, Ohio, USA) or diet supplemented with L-arginine, <i>n</i> -3 EFA, ribonucleotides (Impact® Sandoz Nutrition Corp, Minneapolis, Minn, USA), for first 7 d postoperatively	Supplementation resulted in improved N balances, stimulation of immunity, reduction in wound infections and complications, reduced hospital in-patient stay
Kemen <i>et al.</i> (1995)	Gastrointestinal malignancies	42	Patients received either a standard diet or diet supplemented with L-arginine, <i>n</i> -3 EFA, ribonucleotides (Impact®), for 10 d following surgery	Supplementation resulted in immune stimulation (nos. of T cells, T helper and activated T cells; and increased antibody levels (IgM, IgG) and increased cytokines (IFN $\gamma$ )). Clinically-beneficial effects unknown
Daly <i>et al.</i> (1995)	Upper gastrointestinal and pancreatic cancers	60	Patients randomized to receive either standard enteral nutrition (Traumacal®; Bristol-Meyers Squibb, Evansville, IN, USA) or enteral nutrition supplemented with L-arginine, <i>n</i> -3 EFA and ribonucleotides (Impact®)	Supplementation resulted in reduction in wound infections and/or complications and shorter hospital stay
Moore <i>et al.</i> (1994)	Major trauma (abdomen/ chest)	98	Patients randomized to either Immun-Aid® (McGraw Inc., Irvine, CA, USA; supplemented with L-glutamine, L-arginine, BCAA, <i>n</i> -3 EFA, vitamin E, Zn) or Vivonex TEN®	Patients receiving supplemented diet had increased total lymphocyte count and T helper cells. Clinical benefits of supplementation were fewer intra-abdominal abscesses (0% v. 11%) and less multiple organ failure (0% v. 11%), when compared with non-supplemented patients
Bower <i>et al.</i> (1995)	Sepsis, trauma or following surgery	326	Patients randomized to receive either Impact® or Osmolite HN®, given enterally	Supplementation resulted in a median reduction in hospital stay for all patients of 8 d, for septic patients of 10 d. Significantly fewer nosocomial infections in the nutritionally-supplemented patients. No difference in mortality between the two groups
Gianotti <i>et al.</i> (1996)	Major abdominal surgery	126	Patients randomized to receive standard enteral nutrition, TPN, or enteral nutrition enriched with L-arginine, <i>n</i> -3 EFA, ribonucleic acid	Supplementation resulted in reduced incidence of septic complications and shorter hospital stay when compared with other treatment groups

EFA, essential fatty acids; BCAA, branched-chain amino acids; IgM, IgG, immunoglobulins M and G; IFN $\gamma$ ; interferon- $\gamma$ ; NK, natural killer; LAK, lymphokine-activated killer; CD, cluster of differentiation antigens.

this combination of nutrients on immune function, in intensive care unit patients, were first reported by Cerra *et al.* (1990). This was a small study of twenty patients with either trauma or sepsis or who had undergone elective general surgery. Patients were randomized to receive either a supplemented diet (Impact<sup>®</sup>; Sandoz Nutrition Corp., Minneapolis, MN, USA) or a standard diet, for up to 10 d. It was found that the patients receiving the supplemented diet had enhanced aspects of their immune response when compared with non-supplemented patients.

A larger, multi-centre trial has also investigated the effects of supplementation with L-arginine, RNA and *n*-3 EFA (Impact<sup>®</sup>) in patients who had either undergone surgery, or experienced trauma or had major sepsis, and who required admission to an intensive care unit (Bower *et al.* 1995). Patients (*n* 326) were stratified according to their age and disease (septic or systemic inflammatory response syndrome) and then randomized to receive either a standard diet (Osmolite HN<sup>®</sup>; Ross Laboratories, Columbus, OH, USA) or a diet supplemented with L-arginine, *n*-3 EFA and RNA (Impact<sup>®</sup>), which was given via the enteral route. The results from this study demonstrated that the patients receiving the supplemented diet had a median reduction in hospital stay of 8 d ( $P < 0.05$ ), but for septic patients the median reduction in hospital stay was 10 d ( $P < 0.05$ ). Furthermore, there was a significant reduction in the development of nosocomial infections in the nutritionally-supplemented patients ( $P < 0.01$ ). There was no difference, on the other hand, in mortality rates between the two groups of patients. Other studies have evaluated also the effect of combinations of nutrients on immune function and clinical outcome in a variety of patients, including those in the peri-operative period. These studies have yielded promising results and have been summarized in Table 4. However, some of these studies have been criticised because of differences in N intake and/or provision of trace elements and vitamins between the two groups (nutrients which may also modulate the immune response). However, further well-designed studies evaluating combinations of nutrients are required before their widespread use in clinical practice in patients in the peri-operative period.

#### SUMMARY

In summary, therefore, the provision of TPN to malnourished patients in the pre-operative period reduces the incidence of post-operative complications, but does not affect post-operative mortality. It is likely that the provision of nutrition by the enteral route is as effective as that by the parenteral route, and may have the extra benefit of resulting in a reduction in infectious complications when compared with patients receiving TPN. Furthermore, the use of enteral nutritional support in the post-operative period may also reduce both septic and major complications, but does not alter mortality.

The use of specific combinations of nutrients appears to offer the greatest promise in the use of peri-operative nutritional support. The initial studies reported to date demonstrate reductions in post-operative morbidity, but again there are no benefits on mortality. However, further studies to determine the optimal combinations of nutrients for use in patients in the peri-operative period are urgently required.

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