

Nutritional modulation of gut inflammation

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In the past 25 years, numerous scientific studies have documented the value of nutrient support in critically-ill patients. Sepsis, systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) complicate several surgical diseases and their treatment by surgical, endoscopic, medical and radiological techniques. Many patients who are treated for sepsis receive either intravenous or enteral nutritional support. Administration of these regimens is governed by a sound understanding of the metabolic response to trauma and basic nutritional principles. Strict protocols for administration minimize the technical, mechanical, metabolic, biochemical, haematological and septic complications. Several diseases have a high incidence of septic complications, SIRS and MODS (McCrary & Rowlands, 1993). These include major trauma, obstructive jaundice, inflammatory bowel disease (IBD), acute pancreatitis and major intra-abdominal sepsis. These clinical conditions and their septic complications are characterized by a state of 'hypermetabolism', which leads to a rapid consumption of endogenous stores of protein and energy, immunological dysfunction and deterioration of organ function (Cerra, 1987). These changes, which affect the liver, kidney, gastrointestinal tract, heart and lungs, are orchestrated by a series of neuroendocrine events and the release of cytokines, activators and mediators. The 'gut–liver axis' appears to have a central role in these responses. Altered gastrointestinal structure and function and associated changes in hepatic Kupffer cell function contribute to metabolic dysfunction. Parenteral and enteral nutrient substrates as well as pharmacological and immunological therapies may modify these changes (Cerra, 1991; Wilmore, 1991).

In recent years, there have been two major trends in the use of nutritional support. First, there is a major shift from intravenous administration of nutrients to enteral feeding, which is supported by evidence from controlled clinical trials (Kudsk *et al.* 1992; Moore *et al.* 1992). Second, the quantity of nutrients being administered is decreasing and the quality of the nutrient mix is improving. Enteral feeding may be delivered using normal oral nutrition, standard enteral diets and supplementary enteral nutrition with novel substrates. Substrates suggested as capable of enhancing intestinal integrity and supporting immune function include amino acids (glutamine, arginine and ornithine), fatty acids (short-chain and *n*-3 polyunsaturated) and nucleotides (RNA; Daly *et al.* 1992; Carver & Walker, 1995; Gardiner *et al.* 1995c).

Enteral nutrients produce their beneficial effects in several ways. They support generalized immune function, enhance mucosal barrier function and reduce bacterial translocation. In addition, they may modify hepatic Kupffer cell function, cytokine release and acute-phase protein production. Enteral diets maintain the structural and functional integrity of the small and large bowel by stimulation of motility, mucus production and gastrointestinal hormone release. Maintenance of the lumen milieu of nutrients, micro-organisms and trophic factors is important for normal digestive and barrier function (Silk & Grimble, 1994).

The present paper discusses the experimental evidence of gut mucosal barrier dysfunction in the development of sepsis, SIRS and MODS. IBD can lead to disruption of the gastrointestinal mucosal barrier. Experimental and clinical studies of gut inflammation can provide valuable insights into the pathophysiology of sepsis, SIRS and MODS. A major therapeutic strategy for the prevention and treatment of gut-derived sepsis is the provision of enteral nutrition. Individual speciality nutrients (novel substrates) may have a selective action on the maintenance of gut mucosal integrity (selective gut nutrients) or may support general immune function (immuno-modularity nutrients; Gardiner *et al.* 1995c). The use of these speciality nutrients in critically-ill patients may have beneficial effects on nutritional, metabolic and immune status. This may lead to reductions in complications, length of hospital stay and mortality, but carefully-conducted controlled clinical trials will be necessary to identify those groups of patients most likely to benefit from nutritional interventions (Souba, 1997).

Sepsis, systemic inflammatory response syndrome and multiple organ dysfunction syndrome

Sepsis and related conditions present a gradation of severity of illness. At one end of the spectrum is minimal derangement of normal physiology and rapid restoration of metabolic homeostasis with therapy. At the other extreme is massive disruption of normal organ function, which leads to progressive deterioration and death despite treatment. Central to our understanding of these events is an appreciation that initially there is a localized response to injury. This may lead subsequently to systemic manifestations if the local host defence mechanisms are inadequate or overwhelmed. Localized infections due to bacteria, viruses, fungi and parasites

Abbreviations: IBD, inflammatory bowel disease; MODS, multiple organ dysfunction syndrome; SIRS, systemic inflammatory response syndrome; TNBS, 2,4,6-trinitrobenzene sulfonic acid; TNF, tumour necrosis factor.

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stimulate the release of various mediators, e.g. cytokines, prostaglandins, thromboxanes, platelet-activating factors and the complement system. These help to combat infection by activating neutrophils, with consequent degranulation and release of oxygen radicals which increase local blood flow and vascular permeability allowing the influx of phagocytic cells. They also activate leucocytes and induce chemotaxis. If the severity of the infection is sufficient that these mediators spill over into the systemic circulation, a septic cascade is initiated which may lead to septic shock, SIRS, and MODS (Davies & Hagen, 1997). Superoxide radicals now damage host cells. Endotoxin and various cytokines, activators and mediators, e.g. tumour necrosis factor (TNF), the interleukins, transforming growth factor- β and prostaglandin E_2 all contribute to the initiation and maintenance of this cascade, which may be beneficial or detrimental, depending on the clinical setting.

Sepsis is not synonymous with overwhelming infection, and in many patients who fit the criteria for SIRS, no micro-organism can be demonstrated or cultured (Rowlands, 1997). Our understanding of the development of organ failure and death has expanded greatly since originally described by Baue (1975). We now recognize three stages in the development of SIRS (Bone, 1996a). The balance between the anti-inflammatory systemic response and the pro-inflammatory systemic response is important for metabolic homeostasis, and the disruption of this equilibrium gives rise to a number of syndromes (compensatory anti-inflammatory syndrome, mixed antagonist response syndrome, MODS; see Fig. 1). Their clinical manifestations are cardiovascular compromise

(shock), suppression of immunity, apoptosis and organ dysfunction (Bone, 1996b; Nieuwenhuijzen *et al.* 1996). The importance of cytokines, their natural antagonists and endogenous antibodies to endotoxins in determining outcome in patients with sepsis syndrome has been demonstrated by Goldie *et al.* (1995). This study provides an explanation of why most new immunological therapies have failed to produce clinical improvement in septic patients (Rowlands, 1997).

Gut barrier function in health

The gastrointestinal tract is usually thought of primarily as an organ of digestion and absorption, but it is a metabolically-active organ that requires specific nutrients (Page, 1989). It has a major barrier function, protecting the body from harmful intraluminal pathogens and large antigenic molecules (Saadia *et al.* 1990). In addition, it plays a pivotal role in the metabolism of glutamine (Souba *et al.* 1985). The gut mucosal barrier comprises both immunological and non-immunological protective components, the former being divided into local and systemic components and the latter comprises mechanical and chemical barriers as well as intraluminal bacteria (Table 1). The maintenance of normal epithelial cell structure prevents trans-epithelial migration of particles from the gut lumen, and the preservation of tight junctions between the cells prevents movement through the para-cellular channels (van Leeuwen *et al.* 1994). Acid secretion in the stomach, alkali secretions in the small bowel and mucus production throughout the gastrointestinal tract

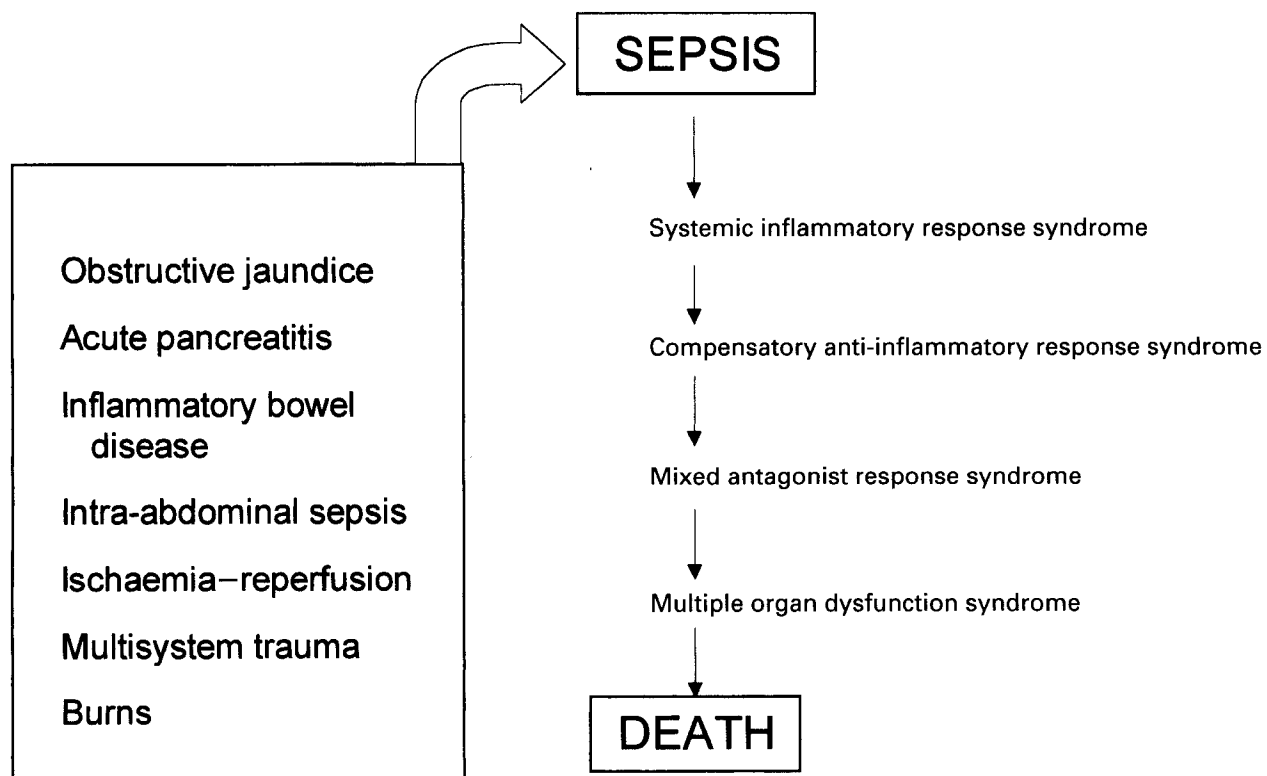


Fig. 1. A number of common surgical conditions have a high incidence of septic complications, which lead to the development of a number of well-recognized syndromes and death.

provides additional protection. The lumen of the gut is colonized by aerobic and anaerobic micro-organisms, and there is a progressive increase in their numbers from the stomach, where gastric acid produces an almost sterile environment, to the colon, which harbours 10⁸ aerobes and 10¹¹ anaerobes. Under normal circumstances, these micro-organisms remain within the lumen of the bowel where they have important functions in metabolic and nutritional homeostasis. In disease states, when the mucosal barrier is compromised, these micro-organisms and their toxic products may 'escape' from the lumen to produce deleterious systemic effects (Fig. 2).

Gut barrier function in disease

The demonstration of intestinal atrophy manifested by changes in weight, structure and mucosal content of DNA and protein has been assumed to indicate impaired intestinal barrier function, but this has not been confirmed in animal studies of protein malnutrition (Deitch, 1990). Recent clinical evidence demonstrates a strong association between compromise of gut barrier function and malnutrition, which suggests a mechanism that facilitates gut-derived infection and sepsis (Reynolds *et al.* 1996; Welsh *et al.* 1998). Dysfunction of the mucosal barrier is thought to result from an imbalance of aggressive and defensive factors on the gastrointestinal mucosa (Sartor, 1990). Genetic and environmental factors may modify the response of the gastrointestinal mucosa to pro-inflammatory factors or may modify the protective factors. Increased gastric acid production, colonization with *Helicobacter pylori*, ingestion of non-steroidal anti-inflammatory analgesics and the use of broad-spectrum antibiotics, predispose the gastrointestinal mucosa to ulceration. Maintenance of mucosal blood flow (Fink, 1991), oxidative fuel supply (Alverdy *et al.* 1988) and a normal intestinal bacterial flora (Barber *et al.* 1991) protect against barrier dysfunction. Failure of the intestinal mucosal barrier results in permeation of microbial and dietary antigens across the intestinal wall. The trans-mural migration of enteric bacteria or their products (endotoxins) to extra-intestinal sites has been termed translocation, and may occur by the trans-cellular or para-cellular routes. Enhanced uptake of macromolecules and bacteria has been demonstrated where the intestinal mucosa is damaged by inflammation, infection,

Table 1. Components of the gut mucosal barrier

Immunological	Non-immunological
Local	Mechanical
Gut-associated lymphoid tissue	Healthy enterocyte
Intra-epithelial lymphocytes	Tight junction
Submucosal aggregates	Cell turnover
Peyer's patches	Normal motility
Mesenteric lymph nodes	Chemical
Secretory IgA	Gastric acidity
Systemic	Salivary lysozyme
Circulatory lymphocytes	Lactoferrin
Hepatic Kupffer cells	Mucus secretion
	Bile salts
	Bacteriological
	Aerobic micro-organisms
	Anaerobic micro-organisms

IgA, immunoglobulin A.

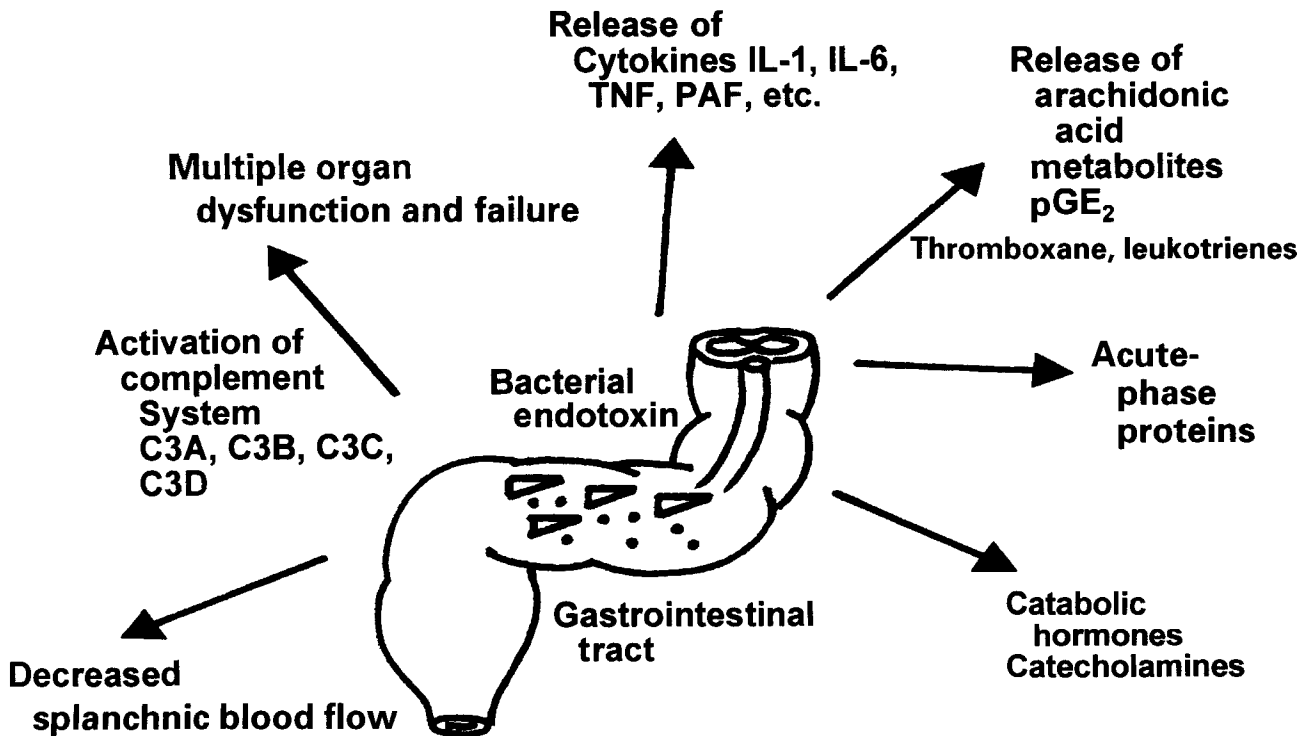


Fig. 2. Various diseases lead to compromise of gut mucosal barrier function. Breakdown of local defences allows translocation of bacteria and toxin. In turn, they activate a number of systemic inflammatory cascades and release of mediators, cytokines, hormones and acute-phase proteins, which further compromise host defences. C3A-D, components of the complement system; IL, interleukin; PAF, platelet-activating factor; PG, prostaglandin; TNF, tumour necrosis factor.

neoplasia or trauma. In addition, systemic endotoxaemia, bacterial translocation, and increased intestinal permeability to macromolecules have been demonstrated in patients with rheumatic diseases, haemorrhagic shock, burns, burn sepsis, major trauma, following chemotherapy or radiotherapy, and in experimental endotoxaemia in the absence of macroscopic intestinal disease. However, translocation of endotoxin or bacteria has not been found commonly in patients after major trauma or burns (Gardiner *et al.* 1995c).

The clinical significance of intestinal mucosal barrier dysfunction is more difficult to determine. Clinical studies strongly suggest that intestinal barrier dysfunction and increased permeability occur in patients with intestinal inflammation and other diseases associated with increased mortality and morbidity. It is hypothesized that translocating micro-organisms and toxins activate a systemic inflammatory cascade and promote organ dysfunction and failure, but it is difficult to demonstrate a causal link (Cerra, 1991).

Gut barrier dysfunction in inflammatory bowel disease

Patients with IBD may exhibit a number of manifestations of malnutrition. They often present with a history of anorexia, nausea, vomiting and abdominal pain, symptoms which are associated with poor nutritional intake. Diarrhoea or high-output fistulas or stomas may lead to significant nutrient losses. There may also be evidence of malabsorption of vitamins, minerals, bile salts, and steatorrhoea with protein loss. Acute depletion of tissue stores of endogenous energy and protein stores occurs rapidly, leading to clinical malnutrition, poor wound healing, weight loss and immune dysfunction. Gut mucosal barrier dysfunction contributes significantly to this state of increased metabolism.

In the Department of Surgery at Queen's University of Belfast, we investigated gut barrier dysfunction in IBD by measuring systemic endotoxin concentrations in patients with quiescent and active disease. In IBD patients requiring hospitalization for acute relapse, systemic endotoxaemia was demonstrated in 88 % of patients with ulcerative colitis (*n* 25), 75 % with indeterminate colitis (*n* 8) and 94 % of those with Crohn's disease (*n* 31). In a group of outpatients with inactive disease, systemic endotoxaemia was demonstrated in 33 % of patients with ulcerative colitis (*n* 33) and in 9 % of those with Crohn's disease (*n* 34; Gardiner *et al.* 1995b). The clinical significance of gut barrier dysfunction in IBD was examined by seeking a correlation between systemic endotoxaemia and disease extent or activity, and by searching for evidence of a specific immune response (production of anti-endotoxin antibodies or the cytokine TNF). Systemic endotoxaemia was found to correlate positively with anatomical extent and clinical activity of ulcerative colitis. Circulating TNF was detected in 40 % of patients with ulcerative colitis and 45 % with Crohn's disease. Plasma TNF and soluble TNF receptor p55 concentrations correlated positively with clinical and laboratory measures of disease activity (Gardiner *et al.* 1995b). In patients with Crohn's disease, there were significant increases in the plasma concentrations of antibodies (immunoglobulin G) to the endotoxin core which were found to correlate positively with systemic endotoxaemia. These findings support a central role for endotoxin in the pathogenesis of IBD (Fig. 3).

The pathogenesis of colonic mucosal barrier dysfunction was investigated in an experimental model of colitis using intraluminal instillation of 2,4,6-trinitrobenzene sulfonic acid (TNBS) and ethanol (Morris *et al.* 1989). This model has been well characterized and possesses clinical

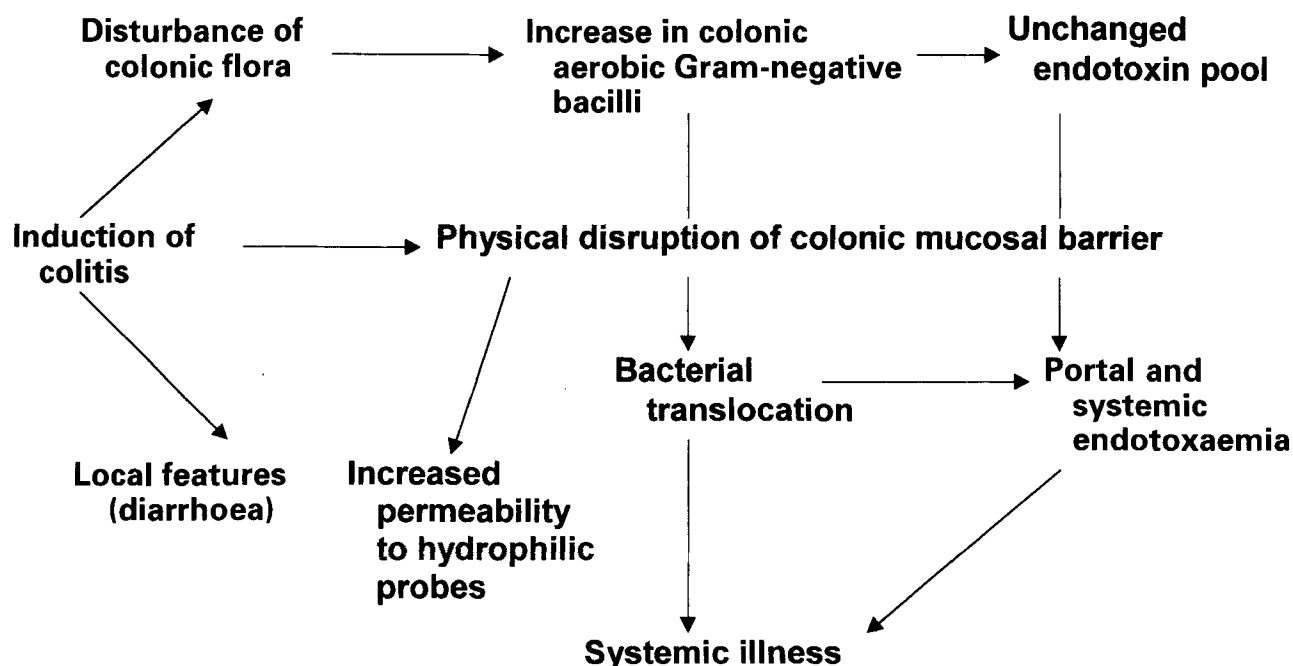


Fig. 3. The pathogenesis of inflammatory bowel disease demonstrating the central role for endotoxin in the development of systemic illness.

biochemical and pathological similarities to colonic Crohn's disease. In this TNBS model, systemic endotoxaemia correlates positively with the macroscopic appearance of the colitis and with serum concentrations of lactate and α_2 -macroglobulin (Gardiner *et al.* 1995a; Neilly *et al.* 1995a). There was an initial reduction in both immunoglobulin G and M anti-endotoxin core antibody, with a subsequent increase. This may represent a consumption of antibody by translocating endotoxin, followed by a B-cell response and an increase in antibody production. Increased colonic permeability to the hydrophilic probe polyethylene glycol (molecular mass 4000) and increase in the translocation of colonic bacteria correlate positively with severity of colitis (Gardiner *et al.* 1995a). A significant increase in the numbers of colonic Gram-negative bacilli and a decrease in the Gram-positive aerobic bacilli count occurred, but there was no effect on the faecal endotoxin load. There was a positive correlation between the severity of colonic inflammation and the extent of bacterial translocation in colitic animals (Gardiner *et al.* 1993). Disruption of the physical barrier is more important than overgrowth of Gram-negative bacilli or release of endotoxin in promoting translocation in experimental colitis.

Treatment of gut mucosal barrier dysfunction

Support of the gut mucosal barrier includes adequate mucosal perfusion, optimal O₂ delivery, prevention of gastrointestinal haemorrhage and maintenance of lumen micro-ecology. These general measures, together with more specific measures, support enterocyte structure and function. An important component of support is enteral nutritional therapy. There is convincing evidence that administration of enteral nutrition when compared with parenteral feeding is associated with improved immune function and reduced septic complications following major trauma. Other treatments that may contribute to resolution are the reduction of the intestinal pool of Gram-negative bacteria and endotoxin, enhancement of mucosal healing, supporting general immune function and neutralizing the systemic effects of bacteria and their toxins (Gardiner *et al.* 1995c).

In IBD, gut barrier dysfunction improves when the intestinal pool of Gram-negative bacteria and endotoxin is reduced by the administration of non-selective or selective antibiotics, of lactulose to promote non-pathogenic lactobacilli, or of adsorbents to bind intraluminal endotoxin. Treatment may be directed at enhancing healing of the intestinal mucosa by administration of anti-inflammatory drugs (steroids) systemically or topically (Neilly *et al.* 1995b). Treatment may be directed at removing or neutralizing extra-intestinal bacteria endotoxin or other cytokines, activators or mediators. Intravenous injection of taurolidine, a drug with antiseptic, antibiotic and anti-endotoxin activity, significantly reduced systemic endotoxaemia in TNBS colitis, whereas systemic broad-spectrum antibiotic (metronidazole and cefuroxime) therapy was ineffective (Gardiner *et al.* 1994). Administration of anti-TNF antibody (cTN3) significantly reduced systemic endotoxaemia, plasma interleukin-6 concentration, acute-phase protein response and weight loss in TNBS colitis. Repair of the intestinal barrier may be hastened by multi-targeted therapy aimed at reducing luminal aggressive

factors, reducing the inflammatory response (steroids, nitric oxide synthase inhibition, anti-cytokines) and selective gut nutrition.

The role of novel substrates in maintaining gut integrity has been extensively reviewed by considering their metabolism in health and disease, the effects on the gut mucosa and the experimental and clinical evidence supporting their use in clinical practice (Gardiner *et al.* 1995c). Evidence that these substrates improve gut mucosal barrier function and increase survival does not necessarily imply that restored barrier function and improved survival are causally linked. The substrates may exert their beneficial effects by improving N balance and metabolism, or by enhancing immune function and clearance of translocated bacteria. From experimental and clinical studies to date the strongest candidates as selective gut nutrients are glutamine for the enterocyte and short-chain fatty acids for the colonocyte. Recent evidence shows that glutamine-supplemented parenteral nutrition improves outcome in critically-ill intensive care unit patients and surgical patients (Griffiths *et al.* 1997; Morlion *et al.* 1998). The results from studies of enteral supplementation of glutamine are disappointing (Powell-Tuck, 1997), and quite modest intakes of standard oral diet (0.6 g N/kg daily) are sufficient to maintain gut integrity and immune function. Short-chain fatty acids and *n*-3 polyunsaturated fatty acids have modest beneficial effects in patients with intestinal inflammation (Ross, 1993). Arginine has proven immunological benefits (Barbul, 1986). Despite this finding, oral supplementation with arginine has been shown to be detrimental in the TNBS-induced colitis model, causing increased colonic inflammation (Neilly *et al.* 1995c), but beneficial to mucosal barrier function and survival after experimental ischaemia-reperfusion injury (Schleiffer & Raul, 1996). There is growing evidence that the L-arginine-nitric oxide pathway is important in the development of colonic inflammation, and that this may lead to new therapeutic strategies in IBD (Kimura *et al.* 1998; Warner & McCartney, 1998). Arginine supplements for critically-ill patients should be used cautiously at present, and there is insufficient evidence from clinical studies to support the use of ornithine, branched-chain amino acid or nucleotide supplementation by themselves. However, there is some evidence that supplementation of enteral diets with combinations of novel substrates is beneficial to patients in a number of different clinical situations where gut barrier function is compromised by malnutrition and hypermetabolism (Bower *et al.* 1995; Daly *et al.* 1995). The use of diets (containing fibre, fermented oats and lactobacillus) that support probiotic bacteria (microbial interference treatment) has been advocated as an important new development in the support of these patients (Bengmark, 1996, 1998).

Summary

Nutritional therapy is an important component of the management of gastrointestinal inflammation, which disrupts the gut mucosal barrier leading to sepsis, SIRS and MODS. Future studies will be needed to define the role of specific nutrients in enhancing mucosal barrier function and supporting general immune function, and how this affects morbidity and mortality of critically-ill patients.

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