DOI 10.1080/13651820310001108

Review article

The role of the intestine in the pathophysiology and management of severe acute pancreatitis

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Background

The outcome of severe acute pancreatitis has scarcely improved in 10 years. Further impact will require new paradigms in pathophysiology and treatment. There is accumulating evidence to support the concept that the intestine has a key role in the pathophysiology of severe acute pancreatitis which goes beyond the notion of secondary pancreatic infection. Intestinal ischaemia and reperfusion and barrier failure are implicated in the development of multiple organ failure.

Discussion

Conventional management of severe acute pancreatitis has tended to ignore the intestine. More recent attempts to rectify this problem have included 1) resuscitation aimed at restoring intestinal blood flow through the use of appropriate fluids and splanchnic-sparing vasoconstrictors or inotropes; 2) enteral nutrition to help maintain the integrity of the intestinal barrier; 3) selective gut decontamination and prophylactic antibiotics to reduce bacterial translocation and secondary infection. Novel therapies are being developed to limit intestinal injury, and these include antioxidants and anti-cytokine agents. This paper focuses on the role of the intestine in the pathogenesis of severe acute pancreatitis and reviews the implications for management.

Keywords

intestine, ischaemia, MODS, pancreatitis, reperfusion, SIRS

Introduction

Severe acute pancreatitis (SAP) remains a significant clinical challenge. It is associated with a mortality rate of 10–40% depending on whether there is sterile or infected pancreatic necrosis [1]. These patients have a profound systemic inflammatory response and usually die with multiple organ dysfunction. A third of deaths occur within days of hospital admission, without an obvious focus of infection [2]. The remaining deaths occur later and are usually the result of secondarily infected pancreatic necrosis (the so-called 'late septic deaths') [3]. Mortality rates have not altered over the last decade [4], and a reduction will only occur when there is a better understanding of the underlying pathophysiology of this disease.

Recent reviews on intestinal barrier dysfunction in acute pancreatitis have focused on bacterial translocation and the intestinal origin of sepsis [5, 6]. However, this paper will explore how the intestine, as both culprit and victim, influences the pathophysiology of SAP (Figure 1). The implications of these interactions with regard to treatment will also be discussed.

The role of the intestine in the development of SIRS/MODS in critical illness

Once considered a quiescent organ, the intestine is now seen to have a pivotal role in the development of the systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) in critical illness [7]. In the 1960s Jacob Fine and his colleagues postulated that severe illness enabled gut organisms and toxins to gain access to the systemic circulation [8]. Wolochow and associates [9] labelled this phenomenon 'bacterial translocation' but it received little attention for 20 years. Renewed interest was generated when it was reported that the intestine might be an important source of infecting microbes in immunocompromised patients [10]. There is now little doubt that bacterial translocation occurs but uncertainty remains over the mechanism

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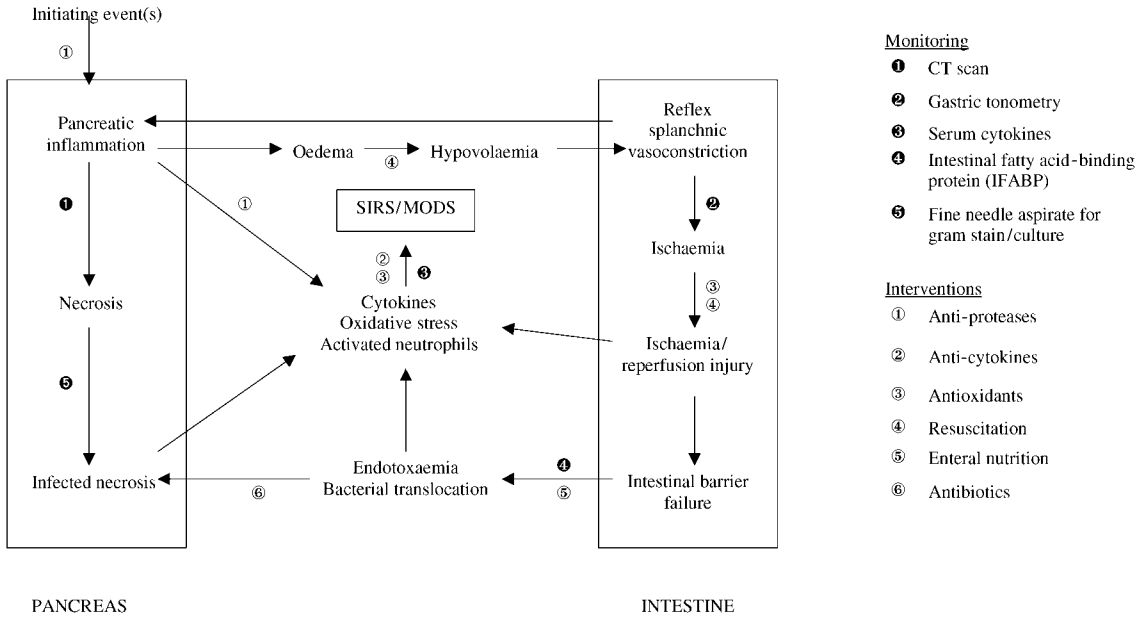

Figure 1. *The interactions between the pancreas and intestine during severe acute pancreatitis with monitoring and interventions used in its treatment.*

and how this relates to MODS [11]. The same bacteria responsible for postoperative septicaemia have been cultured from mesenteric lymph nodes but this does not always lead to SIRS and MODS [12, 13].

Studies of haemorrhagic shock, gram-negative sepsis and trauma have provided an insight into the way that the intestine influences the course of critical illness. The similar systemic manifestations in these diseases suggest common mechanisms that are relevant to severe acute pancreatitis, especially those with late sepsis.

Splanchnic circulation

Acute pancreatitis is characterised by retroperitoneal oedema, 'third space' fluid loss, hypovolaemia and circulatory shock. The physiological response is to prioritise blood flow to vital organs at the expense of the splanchnic circulation. The increased sympathetic outflow that accompanies circulatory shock causes vasoconstriction of the mesenteric post-capillary veins and venules via alpha-adrenergic receptors. This causes an 'auto-transfusion' of up to 30% of the total circulating blood volume, so improving the cardiac output and perfusion of other vital organs [14]. Vasoconstriction of the mesenteric afferent arterioles also occurs but this effect is mediated by the renin-angiotensin axis rather than the sympathetic nervous system [15]. The subsequent increase in systemic vascular resistance also helps to sustain the systemic blood pressure but results in low perfusion through the splanchnic bed.

Splanchnic tissues can adapt to low perfusion states by extracting up to 90% of the oxygen from the blood. This protective effect is limited because prolonged extraction rates of >70% lead to regional ischaemia [16]. Resuscitation does not provide immediate relief, as the splanchnic region is the last to be reperfused [17]. Indeed, patients who appear to be adequately resuscitated, without clinical evidence of hypovolaemia, may continue to suffer from intestinal ischaemia [18]. Intestinal ischaemia can also occur in inflammatory states when the splanchnic blood flow is normal or increased through increased metabolic demand for oxygen [19].

The relationship between intestinal ischaemia and SIRS/MODS has not been fully elucidated, but can be discussed within two broad hypotheses: the 'gut starter' and the 'gut motor' hypotheses.

The 'gut starter' hypothesis is also called the 'two hit model of MODS' and focuses on the role of the neutrophil. Neutrophils are primed as they pass through the mesenteric circulation during reperfusion of the ischaemic intestine. They continue to circulate around the body in this primed yet inactive state until they are provoked by a second insult such as exposure to endotoxin [20]. Priming of the neutrophil is initiated

by mesenteric lymph rather than portal blood and it is the lipid fraction generated by phospholipase A_2 that appears to be most important in priming neutrophils [21]. Neutrophils primed in this way exhibit an increased oxidative burst, augmented release of proteases and cytokines [22], and reduced apoptosis [23] so becoming potent mediators of distant organ dysfunction when activated.

The 'gut motor' hypothesis focuses on the role of the intestinal barrier in the development of SIRS and MODS. When this barrier is disrupted the luminal content invades the portal venous and lymphatic systems. This translocation activates immune cells downstream from the intestinal mucosa, i.e. Peyers patches, macrophages in the lamina propria of the gut, mesenteric lymph nodes and Kuppfer cells in the liver. These activated immune cells release inflammatory mediators that drive the onset of SIRS and MODS even though a focus of infection may not be evident [24].

Components of the intestinal barrier

The intestinal barrier comprises several functional and structural components. These include the intestinal microflora, gut motility, digestive enzymes, unstirred water and mucous layer, epithelial layer, endothelial layer, mucosal associated lymphoid tissue and the gut-liver axis. The most critical is the epithelial layer. It comprises a single layer of columnar cells arranged into villi and crypts. Microvilli line the apex of the cell and provide a barrier to microbes by virtue of the small space between microvilli and a negative charge [25]. Tight junctions encircle the apical pole (the zonula occludens) connecting adjacent cells by strands that are linked to the cell cytoskeleton [26]. These prevent passage of molecules >11.5 Å in radius [27], that include lipopolysaccharide and many other bacterial proinflammatory mediators.

Disruption of the intestinal barrier

Ischaemia increases the permeability of the intestinal barrier and there is mucosal acidosis (possibly by lipid peroxidation from free radicals) [28] and ATP depletion [29]. As the ischaemia worsens, epithelial cells separate from the tips and then the sides of the villus [30]. Surviving cells develop an increased rate of apoptosis [31] and decreased nutrient transport [32]. Eventually the lamina propria disrupts resulting in mucosal ulceration, haemorrhage and transmural necrosis.

The intestinal barrier is particularly susceptible to ischaemia because of the anatomy of the villus microcirculation. The countercurrent arrangement of veins around a central arteriole allows for arteriovenous shunting of oxygen and anoxia of the villus tip [33]. This effect is exacerbated by haemodilution due to plasma skimming of central arterioles that branch off at right angles from their parent vessel [34].

Ischaemia causes hypoxanthine to accumulate and ATP is depleted through inadequate oxidative phosphorylation. In addition, xanthine dehydrogenase is converted to xanthine oxidase. When blood flow is restored xanthine oxidase converts hypoxanthine to xanthine with the liberation of the superoxide ion. The superoxide ion leads to the formation of further oxygen free radicals that injure cell membranes by lipid peroxidation [35]. Thus, intestinal reperfusion causes further damage through the production of oxygen free radicals and inflammatory mediators.

Oxygen free radicals are also chemoattractant for neutrophils, and along with other stimuli (i.e. TNF-α IL-1, IL-8, GM-CSF, IFN-γ, leukotriene B4, platelet activating factor (PAF), ICAM-1, ELAM-1, and complement C3a and C5a) initiate migration of activated neutrophils into the reperfused tissue [36].

The accumulation of activated neutrophils may be the main cause of intestinal injury, and they mediate damage in three ways: enhancing the ischaemic effect, releasing of oxygen free radicals and proteases, and amplifying the inflammatory response.

When the endothelial cell is stimulated by cytokines, oxygen free radicals, complement or thrombin, it expresses adhesion molecules that bind activated neutrophils. These aggregate at the pre-capillary sphincter and impair blood flow. The accumulation of platelets, products of the coagulation pathway and cellular debris amplifies this effect and the result increases the ischaemia [37].

Oxygen free radicals derived from activated neutrophils are produced by cell surface nicotinamide adenine dinucleotide phosphate oxidase and intracytosolic myeloperoxidase. Direct intestinal injury is caused by the release of lyzozymes containing neutral serine proteases that degrade elastin, collagen I, II, III and IV, fibrinogen, fibronectin and proteoglycans, and metallo-proteases

(MMP-1, MMP-2, MMP-3) that digest collagen, gelatin and proteoglycans [38].

Neutrophils amplify the inflammatory response by secreting a wide range of mediators. When activated they release proinflammatory (IL-1, TNF-α, IL-6, IL-8, IFN-γ) and anti-inflammatory (TGF-β) cytokines and their antagonists (IL-1ra) [39]. In addition they activate platelets and coagulation cascades, and inhibit fibrinolysis [40].

Intestinal injury is also mediated through the complement system by the membrane attack complex [41]. Complement can attract neutrophils [42], stimulate their migration across endothelial cells [43], increase myeloperoxidase activity and the production of cytokines [44], and can mediate damage in distant organs [45].

Cytokines that are liberated from the intestine during ischaemia-reperfusion can directly affect the intestinal barrier. TNF-α induces the permeability of intestinal epithelial [46] and endothelial cells [47] by altering the actin cytoskeleton [48]. Blockade of TNF-α significantly reduces the extent of bacterial translocation [49]. IFN-γ increases nitric oxide production [50] that inhibits the Na+,K+-ATPase pump [51] so increasing the permeability of model epithelial cells [52]. The effects of IFN-γ are further enhanced by TNF-α [53] but limited by IL-10 [54]. IL-4 also increases epithelial permeability [55].

Phospholipase A_2, found in high concentration in the intestinal mucosa, plays an important role in mucosal injury and translocation [56]. It is excessively activated in intestinal ischaemia [57] and in sepsis is released under the partial control of TNF-α [58]. It generates proinflammatory lipid mediators such as platelet activating factor that stimulates endothelial cells and neutrophils, enhancing neutrophil-mediated tissue injury. It also generates arachidonic acid so liberating eicosanoids that cause direct tissue injury [59].

Nitric oxide (NO) has been shown to have both a protective [60] and injurious effect [61] on the intestinal barrier. Under normal conditions it is an antioxidant and a signalling molecule that maintains intestinal microcirculation. But during ischaemia and reperfusion, NO is converted to cytotoxic nitrites by superoxide radicals. One such nitrite, peroxynitrite, activates poly(ADP-ribose) synthetase by breaking single strands of DNA. This nuclear enzyme then depletes enterocyte NAD+ and ATP and increases intestinal permeability [62]. The large concentrations of NO liberated from the intestine during ischaemia and reperfusion are probably due to an upregulation of inducible NO synthase (iNOS) [63]. Blockade of iNOS prevents the increased intestinal permeability [64] and mesenteric vascular hyporeactivity [65] caused by endotoxin. It also limits bacterial translocation during intestinal ischaemia and reperfusion [66].

Evidence of impaired intestinal function in acute pancreatitis

There is increasing evidence that the pathophysiologic mechanisms outlined above are relevant to acute pancreatitis. This suggests that the intestine is not only adversely impacted by acute pancreatitis, but plays a role in its progression.

Intestinal atrophy with nutritional depletion

Traditional management of acute pancreatitis has aimed to rest the pancreas, by keeping the patients 'nil by mouth'. It is now recognised that the intestines require intraluminal nutrition for the maintenance of their structure and function. Fasting leads to intestinal mucosal atrophy [67], increased rate of enterocyte apoptosis [68], decreased glutamine and arginine transport [69], and altered mucin composition of goblet and deep crypt cells [70]. These changes result in a breakdown of the intestinal barrier as evidenced by increased intestinal permeability [71].

Intestinal ischaemia

Acute pancreatitis reduces intestinal blood flow [72], resulting in mucosal acidosis. Gastric tonometry enables calculation of the intramucosal pH (pHi) by measuring the partial pressure of carbon dioxide in the lumen and the bicarbonate in the blood. This indirect measurement of the adequacy of intestinal perfusion has become a valuable tool in a number of clinical contexts and it has been validated in low flow states [73]. In a series of patients with acute pancreatitis the pHi was more closely related to MODS and death than to APACHE II, arterial pH, mixed venous pH, lactic acid and oxygen delivery and consumption. The pHi within 48 hours of intensive care admission was lower in those who died than in those who survived. A pHi of 7.25 or lower predicted death with an overall accuracy of 82% [74].

Intestinal barrier failure and translocation

The alterations in the intestinal barrier function observed during circulatory shock and sepsis models have been identified in acute pancreatitis. An increase in intestinal permeability has been reported in animal pancreatitis [75] and the degree of permeability correlated with the severity of pancreatitis [76]. This has been confirmed in human studies where increased intestinal permeability occurred early in pancreatitis [77], was more likely to be seen in those with MODS [78], and normalised during recovery [79]. It is unclear whether the changes in intestinal permeability contribute to the development of more severe pancreatitis or are just a consequence of it.

One way that the changes in the intestinal barrier may influence the course of pancreatitis is in secondary infection of pancreatic necrosis. These infections are usually due to bacteria, both aerobic and anaerobic, of a similar spectrum to intestinal microflora [80]. Bacterial translocation from the intestine is well documented in experimental acute pancreatitis but the mechanism is still unclear [81]. Human studies demonstrating increased permeability have not demonstrated an increased incidence of septic complications. Furthermore, the increased permeability occurred early but the peak incidence of infection is known to be 3 weeks into the course of the disease.

Acute pancreatitis may enhance bacterial translocation by altering intestinal motility. Ileus promotes a change in the intestinal microflora and bacterial overgrowth leading to translocation [82]. Pancreatitis delays intestinal transit time [83] and this has been identified as a contributing factor in translocation during experimental pancreatitis [84].

Endotoxaemia

Animal studies have shown that pre-treatment with low dose lipopolysaccharide (50 μg/kg) mitigates the formation of pancreatic oedema, lowers the serum amylase [85], upregulates acinar cell apoptosis and reduces the severity of caerulein pancreatitis [86]. Acinar cell apoptosis appears to have a protective role, as it is inversely related to the severity of pancreatitis in several different models [87]. Pancreatic PAF and phospholipase A_2 may be the triggers of this apoptosis [88, 89]. While these studies suggest that the pathological features of acute pancreatitis might be modified by endotoxaemia through the induction of acinar cell apoptosis, there are other studies that suggest that endotoxaemia exacerbates experimental pancreatitis [90]. For instance, intraperitoneal injection of endotoxin (0.5 and 1.0 mg/100 g) transformed experimental acute pancreatitis (duct ligation and arginine models) to a more severe form [91].

Endotoxaemia appears to correlate with the severity, incidence of systemic complications and mortality rates of acute pancreatitis in patients [92]. The usefulness of measuring endotoxaemia is limited by its intermittent appearance in the peripheral circulation. Another approach is to measure the endogenous antibodies to endotoxin, both IgM and IgG. It has been shown that endotoxaemia occurs in almost all patients with severe acute pancreatitis by the significant decrease and/or depletion of IgM anti-endotoxin antibodies. Similar changes in the serum levels of IgG anti-endotoxin antibody accurately predict death in patients with severe acute pancreatitis [93].

Implications for management: towards an intestinal focus

The conventional management of acute pancreatitis has given scant regard to the intestine, and as a result may increase disease severity. As discussed, initial resuscitation may not overcome splanchnic hypoperfusion, and aggressive resuscitation may enhance reperfusion injury. Inotropic support may further compromise the intestine [94] and keeping the patient nil by mouth for even short periods leads to sloughing of enterocytes, villus atrophy and increased intestinal permeability.

In the light of the emerging evidence regarding the role of the intestine in acute pancreatitis there is a need to re-evaluate the approach to management so that there is an emphasis on the preservation of intestinal integrity and function. In particular there should be recognition of the need for sufficient resuscitation to overcome intestinal ischaemia and for adjunctive measures to reduce reperfusion injury and loss of the intestinal barrier. Whether cytokine-based therapies will have a clinical role in preserving intestinal integrity and function has yet to be determined [95].

Fluids and endpoints for resuscitation

The rapid restoration and maintenance of intravascular

fluid volume remains one of the few therapeutic measures generally accepted as effective in the management of acute pancreatitis [96]. Improvements in fluid resuscitation, oxygen delivery and intensive care mean that patients are more likely to avoid acute renal failure and survive the initial hypovolaemic insult [97]. A significant proportion will still go on to develop early multiple organ failure and death [98].

The standard clinical parameters used to monitor the resuscitation of hypovolaemia, i.e. heart rate, blood pressure, urine output and haemoglobin, do not detect the residual mesenteric hypoxia [99]. The extent of this hypoxia is difficult to estimate clinically, even for experienced intensive care physicians [100]. The search for an appropriate endpoint in resuscitation has led to the gastric tonometer as an indirect marker of the adequacy of intestinal perfusion. Although it appears to be a sensitive predictor of outcome in the critically ill, its role in guiding resuscitation is not well established. Further studies are required to determine whether tonometric guided resuscitation will improve management of patients with acute pancreatitis [101].

There is some evidence that cardiac preload (measured as right ventricular end diastolic volume (RVEDV) index by means of a pulmonary artery catheter) may be a better guide to resuscitation. It has been shown that splanchnic perfusion and outcome improved in trauma patients resuscitated to a RVEDV index $>100\ ml/m^2$. This approach appears to be more effective than inotropic support and is less likely to impact pulmonary function [102].

Less invasive methods of monitoring the effects of resuscitation include skeletal muscle monitoring. Multiparameter fiberoptic sensors placed in the deltoid detect PCO_2 and evidence suggests that is a better guide than the restoration of PAO_2 [103].

Bioimpedence is a recently developed technique that records an alternating electrical current of high frequency and low amplitude through limb electrodes. Resistance is due to water and electrolytes and vector analysis is used to determine changes in resistance and hence fluid balance. It has been validated as an accurate measurement of central venous pressure [104] and cardiac output [105] in critically ill patients.

The most appropriate resuscitation fluid in acute pancreatitis has not been determined. Impairment of the pancreatic microcirculation and the development of pancreatic necrosis are not prevented by conventional resuscitation using crystalloid [106]. Furthermore, lactated Ringer's solution has been shown to be proinflammatory, inducing cell activation and expression of genes involved in inflammation, cell migration and tissue remodelling [107]. Ringer's ethyl pyruvate solution (REPS) is a novel resuscitation fluid that replaces the lactate in lactated Ringer's with the stable form of pyruvate. Pyruvate is a potent antioxidant and it has been shown to ameliorate the structural and functional damage to rodent intestinal mucosa following mesenteric ischaemia-reperfusion [108]. Its effect in pancreatitis has yet to be determined.

Hypertonic saline may be a more immediate alternative to lactated Ringer's due to its immunosuppressive properties. It abrogates neutrophil priming by inhibiting the intracellular signalling pathways by cell shrinkage [109], and enhances the protective function of T cells [110]. It has been shown to attenuate end-organ damage during rodent pancreatitis [111] and limits bacterial translocation during haemorrhagic shock [112]. However, in a clinical trial of burn patients hypertonic saline led to increased renal failure and mortality, casting doubt on its safety in restoring volume deficits [113].

Dextran is a colloid that improves pancreatic microcirculation, reduces trypsinogen activation, prevents acinar necrosis and improves survival of necrotising pancreatitis in rats [114]. A phase-I study has suggested that these effects are relevant to patients [115]. A major disadvantage, however, is its tendency to be coagulopathic by reducing platelet adhesiveness, depressing factor VII and inhibiting fibrinolysis [116]. This has led to calls for its abandonment as a resuscitative fluid [117].

The role of artificial blood substitutes is still to be defined. Diaspirin cross-linked haemoglobin restores the pancreatic microcirculation during hypovolaemic shock [118], improves mucosal perfusion in rodent ileum during sepsis [119] and abrogates pathologic post-injury neutrophil cytotoxic function [120]. However, its clinical application has been halted by two trials where mortality was increased following its use in stroke [121] and trauma victims [122]. Trauma trials with other groups of blood substitutes (that use polymerised haemoglobin rather than cross-linked) have been encouraging [123], and further trials with bovine and recombinant haemoglobin are still in progress.

Low molecular weight heparin used during resuscita-

tion has been shown to prevent mesenteric neutrophil rolling and adhesion that may modulate the damaging effects of the early inflammatory response [124]. Other resuscitation therapies include those aimed at correcting the splanchnic vasoconstriction. The use of enalapril, an angiotensin-converting enzyme inhibitor, improves intestinal perfusion in the critically ill [125]. The use of oestradiol in rodent models of haemorrhagic shock and sepsis also improved intestinal perfusion if given at the beginning of resuscitation, but had no effect on systemic oxygen consumption or cardiac output [126]. Further studies are required to determine whether these therapies have a role in the treatment of pancreatitis.

Inotropes and selective splanchnic vasoconstriction

The use of inotropes to maintain systemic arterial blood pressure has come under scrutiny because of their effect on intestinal blood flow. Adrenaline is not recommended in septic shock as it impairs intestinal perfusion and leads to gut mucosal damage [127]. Dobutamine has a variable effect, and fails to improve intestinal blood flow when measured by regional catheterisation and dilution dye test [128]. In contrast noradrenaline enhances intestinal oxygen utilisation as measured by pHi [129]. Low dose dopamine increases the intestinal blood flow and oxygen delivery providing the fractional intestinal flow is not already high before treatment [130].

Dopexamine, a dopaminergic and beta-adrenergic agonist, improves intestinal perfusion and oxygenation [131], and maintains intestinal villus microcirculation during normotensive endotoxaemia [132]. Like dopamine, however, it does not improve intestinal oxygenation in states of hyperdynamic septic shock where the intestinal flow is already increased [133].

The appropriate inotrope for patients with severe acute pancreatitis has yet to be determined. The use of alpha-adrenergic agonists exacerbates rodent pancreatitis by reducing microcirculatory flow in the pancreas [134]. However, beta-adrenergic and dopaminergic stimulation improve pancreatitis through reduction in the microvascular permeability [135]. The consequences of indiscriminate inotrope use on intestinal and pancreatic circulation need to be recognised. There is a need for selectivity to preserve intestinal circulation and enhance pancreatic perfusion.

Enteral nutrition and preventing intestinal barrier failure

Acute pancreatitis is characterised by hypermetabolism [136] and there has been strong advocacy for total parenteral nutrition [137]. This has been based on the premise that 'gut rest' and the 'avoidance of pancreatic stimulation' are important to the management of acute pancreatitis. However, human studies show that jejunal feeding only results in minimal increases in pancreatic enzyme, bicarbonate and volume output [138] and may even suppress enzyme production [139]. In experimental models enteral feeding attenuates caecal bacterial overgrowth [140], maintains the immune responsiveness of the host [141], preserves intestinal mucosal integrity [142] and permeability [143], and prevents bacterial translocation [144].

Clinical trials comparing parenteral and enteral nutrition have shown the latter to reduce the inflammatory response, disease severity [145], and the rate of septic complications in acute pancreatitis [146]. Furthermore parenteral nutrition does not hasten the resolution of acute pancreatitis and it is significantly more expensive than enteral feeding [147]. As a result enteral feeding has become the preferred mode of nutritional support for patients with acute pancreatitis. The most beneficial enteral nutritional formula has yet to be determined, but enteral feeds fortified with immune-enhancing substances (e.g. glutamine, arginine and omega-3 fatty acids) may decrease the length of hospital stay and septic complications in patients with pancreatitis [148].

Parenteral nutrition does have a role, however, in some patients who cannot tolerate the full requirement of protein and calories by enteral means [149]. In these cases, only a small volume of low residue enteral diet is required to protect the intestinal mucosa [150].

Prevention of secondary infections

Infection of necrotic pancreas by enteric bacteria is a key determinant of clinical outcome [151]. Reducing microflora overgrowth by restoring gut motility reduces bacterial translocation and improves outcome in acute pancreatitis [152]. Animal studies have shown a decrease in pancreatic infection and mortality with the use of either oral antibiotics to selectively decontaminate the gut [153, 154], or intravenous antibiotics with high pancreatic tissue penetration [155, 156]. Similar studies

in humans have shown benefits from both systemic antibiotics and selective gut decontamination [157].

Early prospective randomised trials that used antibiotics in necrotising pancreatitis showed a reduction in pancreatic infection although mortality was not altered [158–160], except for one study that used selective gut decontamination with norfloxacin, colistin and amphotericin [161]. An early meta-analysis that included these four studies did show a reduced overall mortality [162] and this has been supported by a more recent meta-analysis [163].

A broad-spectrum antibiotic that achieves therapeutic pancreatic tissue levels is important. Imipenem is most widely used because it has been shown to reduce pancreatic infection and mortality [164]. In addition, it appears to reduce the need for surgery and the overall number of major organ complications in acute necrotising pancreatitis [165]. The current recommendation is to administer imipenem-cilastin for 2–4 weeks once the diagnosis of necrotising pancreatitis has been made [166].

Concerns over multi-resistance and fungal infections have arisen with the more widespread use of antibiotic prophylaxis. A recent prospective study revealed that 24% of pancreatic infections are due to fungi, but these are easily controlled. Infection with multi-resistant organisms was rare but significant as it led to a negative outcome [167].

On the basis of available evidence many centres consider that early antibiotic prophylaxis is mandatory in the management of severe acute pancreatitis to reduce secondary infections by enteric organisms. Questions still remain, however, over its role in less severe forms of pancreatitis.

Novel therapies

The complex cytokine interactions and inflammatory pathways which mediate SIRS/MODS in acute pancreatitis are being unravelled and may provide potential sites for intervention [168]. Blocking a single cytokine or inflammatory mediator is unlikely to be successful owing to the large redundancy in these pathways [169]. There is a current trend to target multiple sites, and it will be necessary to give consideration to the balance between the pro- and anti-inflammatory responses in any intervention strategy [170].

Antioxidant therapy

Antioxidant therapy in acute pancreatitis needs to be formally evaluated in a randomised controlled clinical trial. A series of prospective studies have demonstrated that significant oxidative stress occurs within 48 hours of the onset of symptoms and that it is correlated with the severity of acute pancreatitis [171–174]. While the source of the reactive oxygen species will include activated neutrophils, it is likely that the intestinal ischaemia and reperfusion also contribute. Bolstering the antioxidant defences should be of benefit, especially during resuscitation when there is the risk of reperfusion injury. As demonstrated in a study of lower limb ischaemia reperfusion, patients with a low antioxidant reserve are at an increased risk of developing SIRS in the postoperative period [175].

Antioxidants that have improved the outcome of animal models of pancreatitis include N-acetylcysteine [176], melatonin [177], lazaroid [178] and taurine [179]. Human trials with mannitol (a hydroxyl scavenger) and folate (xanthine oxidase inhibitor) along with splanchnic perfusion support decreased the incidence of MODS in critically ill patients [180]. The addition of intravenous lidocaine, vitamin C, selenium, polymyxin B (reduces endotoxin) and hydrocortisone, and enteral administration of glutamine, acetylcysteine, and vitamins A and E reduced the mortality and length of ICU stay [181]. Such a 'shotgun approach' to therapy fails to isolate the relative benefit of each component, but does highlight the need for further clinical trials of antioxidant therapy in acute pancreatitis.

Anti-cytokine therapy

Almost all the experimental studies examining the effects of anti-cytokine therapies in acute pancreatitis have neglected the effect on the intestine and the intestine-derived cytokine response [182].

TNF-α and IL-1 are important mediators in SIRS and probably play a role in the early stages of acute pancreatitis. Strategies aimed at blocking these cytokines in human sepsis trials have been disappointing [183, 184] but the recent discovery of a single allele in the TNF-α promotor region that is associated with increased risk for sepsis may help explain the broad range of observed responses [185]. Improved survival and lung function follow pretreatment with anti-TNF polyclonal antibody

in rodent pancreatitis [186]. Delayed antagonism of TNF-α may be more effective than early treatment, because of the beneficial effect TNF-α has on regulating the quiescent immune system [187]. IL-1 blockade with the naturally occurring receptor antagonist, IL-1ra, attenuates the release of TNF-α, IL-6, amylase, lipase, neutrophil accumulation in the lung, and pancreatic damage in rodent necrotising pancreatitis. Mortality was decreased if IL-1ra was given prophylactically [188].

IL-10 is a natural anti-inflammatory cytokine that reduces the release of TNF-α, IL-1B and IL-6 when given to caerulein-induced rodent pancreatitis [189]. It also reduces the mortality in diet-induced mouse pancreatitis [190]. Successful transcription of the IL-10 gene into murine pancreas by means of a plasmid/liposome vector also decreased the severity of pancreatitis [191]. Two randomised studies have been performed to assess the efficacy of IL-10 in preventing post-ERCP pancreatitis [192, 193]. Results were conflicting and the study showing benefit had a particularly high rate of post-ERCP pancreatitis (30%). Further studies are warranted.

Platelet activating factor is a biologically active phospholipid that is activated by phospholipase A_2. It is released from neutrophils, macrophages, platelets and endothelial cells and is an important mediator in the inflammatory processes. It causes intestinal barrier dysfunction by upregulating intestinal enzyme activity and gene expression of phospholipase A_2 [194]. Antagonism of PAF attenuates intestinal barrier dysfunction in rodent pancreatitis [195], thereby reducing bacterial translocation [196]. It also reduced lung changes [197] and mortality [198]. Randomised trials on humans with septic shock have shown reduced organ dysfunction and morbidity when treated with a PAF antagonist [199]. These improvements have not been confirmed in a human trial of severe acute pancreatitis, where PAF antagonism failed to prevent new onset of organ failure or reduce mortality [200].

Other novel therapies aim at the cell adhesion molecules. Treatment with monoclonal antibodies to ICAM-1 and PECAM-1 reduces IL-1 release and leukocyte recruitment so maintaining endothelial barrier function [201]. Lung injury is ameliorated [202] as is local pancreatic damage [203]. Lung injury can also be prevented in animal pancreatitis by blocking the signals to prime neutrophils that are released by macrophages. Antibodies and carboxamide derivatives have been used to block cytokine-induced neutrophil chemoattraction and result in less lung damage. Unfortunately they do not reduce pancreatic damage [204, 205].

It can be expected that therapies based on a better understanding of the cytokine events underpinning severe acute pancreatitis and its attendant MODS will be developed to limit intestinal dysfunction and improve clinical outcome.

Monitoring intestinal function in acute pancreatitis

The wider recognition of the role of the intestine in the pathophysiology of acute pancreatitis provides the impetus to identify markers of intestinal integrity and function that will have clinical and research utility. Intestinal mucosal acidosis, for instance, indicates ongoing splanchnic hypoperfusion, and has been used to predict organ failure and death in critically ill patients [206].

The use of tonometry has already been discussed. The pHi has been used as an index of adequacy of resuscitation after trauma, where it provided an early warning of systemic complications in the post-resuscitation period [207]. There are still doubts over its accuracy in assessing splanchnic mucosal blood flow but the importance of monitoring the gastric pHi has been highlighted. A recent modification to the tonometric method has been a recognition that pHi may be replaced by intramucosal pCO_2 or the gradient of intraluminal to end-expired $paCO_2$ [208].

Markers of intestinal barrier failure that may prove useful are D-lactate, intestinal fatty acid-binding protein (IFABP) and calcitonin precursors. D-Lactate is a stereoisomer of mammalian L-lactate and it is strictly the product of bacterial fermentation. The fact that the liver does not metabolise it means that peripheral levels reflect portal venous levels. It has been shown to have discriminatory value in the diagnosis of mesenteric ischaemia in a prospective clinical study [209]. IFABP is uniquely located in the cytoplasm of mature enterocytes of the small intestine and has been shown to be a sensitive marker of intestinal ischaemia and SIRS [210]. Studies have shown that there is a significant increase in IFABP in the serum of patients with severe acute pancreatitis [211]. CTpr, a serum calcitonin precursor, is also raised in severe acute pancreatitis, the concentra-

tion of which correlates with the degree of intestinal permeability [212].

The use of the polymerase chain reaction (PCR) to identify bacterial DNA fragments in the circulation may yet prove useful as an historical marker of bacterial translocation [213]. At present this approach is too sensitive, as the DNA detected represents live invading organisms, dead pre-absorbed organisms and the aftermath of bacterial phagocytosis.

Conclusion

Severe acute pancreatitis is associated with impaired intestinal function. Intestinal dysmotility, ischaemia, hyperpermeability, bacterial translocation and endotoxaemia are all features of the disease. Better understanding of the pathophysiological role of the intestine in acute pancreatitis will result in new treatment paradigms warranting careful evaluation.

It is likely that a management approach will emerge to include resuscitation aimed at restoring intestinal blood flow and oxygenation through the use of appropriate fluids, inotropic agents and monitoring. The addition of antioxidant therapy will help to reduce free radical-mediated reperfusion injury. The integrity of the gut barrier will be further enhanced by therapies aimed at dampening the local inflammatory response, and early enteral nutrition of an appropriate formula. Prophylactic antibiotics and selective gut decontamination will help prevent the added insult of secondary infections.

More is known about the impact of the intestine on the course of acute pancreatitis, than on the impact of acute pancreatitis on the intestine. It is reasonable to assume that there is a reciprocal impact. The management of acute pancreatitis needs to better reflect the important role of the intestine in its pathophysiology.

References

1 Baron T, Morgan D. Acute necrotizing pancreatitis. *N Engl J Med* 1999;**340**:1412–17.

2 Secchi M, Raimundo G, Quadrelli L, Tagliaferri E, Brogliatti M, Nosti A. Fulminant pancreatitis. *Br J Surg* 1998;**85**:80.

3 Tran D, Cuesta M, Schneider A, Wesdorp R. Prevalence and prediction of multiple organ system failure and mortality in acute pancreatitis. *J Crit Care* 1993;**8**:145–53.

4 Flint RS, Windsor JA, Bonham M. Trends in the management of severe acute pancreatitis: interventions and outcomes (accepted Aust. NZ. J. Surg).

5 Andersson R, Wang XD. Gut barrier dysfunction in experimental acute pancreatitis. *Ann Acad Med Singapore* 1999;**28**:141–6.

6 Foitzik T. The enteral factor in pancreatic infection. *Pancreatology* 2001;**1**:217–23.

7 Marshall J, Christou N, Meakins J. The gastrointestinal tract: the undrained abscess of multiple organ failure. *Ann Surg* 1993;**218**:111–19.

8 Cardis DT, Reinhold RB, Woodruff PWH, Fine J. Endotoxaemia in man. *Lancet* 1972;**2**:1381.

9 Wolochow H, Hildebrand GJ, Lammanna C. Translocation of microorganisms across the intestinal wall in rats: effect of microbial size and concentration. *J Infect Dis* 1966;**116**:523.

10 Tancrede CH, Andremont AO. Bacterial translocation and gram negative bacteremia in patients with hematologic malignancies. *J Infect Dis* 1984;**150**:699.

11 Lemaire LC, van Lanschott JJ, Stoutenbeek CP, van Deventer SJ, Wells CL, Gouma DJ. Bacterial translocation in multiple organ failure: cause or epiphenomenon. *Br J Surg* 1998;**84**:1340–50.

12 MacFie J, O'Boyle C, Mitchell CJ, Buckley PM, Johnstone D, Sudworth P. Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. *Gut* 1999; **45**: 223–8.

13 Kanwar S, Windsor AC, Welsh F, Barclay GR, Guillou PJ, Reynolds JV. Lack of correlation between failure of gut barrier function and septic complications after major gastrointestinal surgery. *Ann Surg* 2000;**231**:88–95.

14 Reilly PM, Wilkins KB, Fuh KC, Haglund U, Bulkley GB. The mesenteric hemodynamic response to circulatory shock: an overview. *Shock* 2001;**15**:329–43.

15 Aneman A, Svensson M, Broome M, Biber B, Petterson A, Fandriks L. Specific angiotensin II receptor blockade improves intestinal perfusion during graded hypovolaemia in pigs. *Crit Care Med* 2000;**28**:818–23.

16 Rowell LB, Blackmon JR, Kenny MA, Escourrou P. Splanchnic vasomotor and metabolic adjustments to hypoxia and exercise in humans. *Am J Physiol* 1984; **247**:H251–8.

17 Biffl W, Moore E. Splanchnic ischemia/reperfusion and multiple organ failure. *Br J Anaesth* 1996;**77**:59–70.

18 Ruokonen E, Usaro A, Alhava E, Takala J. The effect of dobutamine infusion on splanchnic blood flow and oxygen transport in patients with acute pancreatitis. *Intensive Care Med* 1997;**23**:732–7.

19 Dahn MS, Lange P, Lobdell K, Hans B, Jacobs LA, Mitchell RA. Splanchnic and total body oxygen consumption differences in septic and injured patients. *Surgery* 1987;**101**:69–80.

20 Moore E, Moore F, Francoise R, *et al*. The post ischemic

gut serves as a priming bed for circulating neutrophils that provoke multiple organ failure. *J Trauma* 1994;**37**:881–7.
21 Gonzalez RJ, Moore EE, Ciesla DJ, Biffl WL, Offner PJ, Silliman CC. Phospholipase A(2)-derived neutral lipids from posthemorrhagic shock mesenteric lymph prime the neutrophil oxidative burst. *Surgery* 2001;**130**:198–203.
22 Zallen G, Moore EE, Johnson JL, *et al*. Circulating post-injury neutrophils are primed for the release of pro-inflammatory cytokines. *J Trauma* 1999;**46**:42–8.
23 Biffl WL, Moore EE, Zallen G, *et al*. Neutrophils are primed for cytotoxicity and resist apoptosis in injured patients at risk for multiple organ failure. *Surgery* 1999; **126**:198–202.
24 Meakins JL, Marshall JC. The gastrointestinal tract: the "motor" of multiple organ failure. *Arch Surg* 1986;**121**: 196–208.
25 Jacobs LR. Biochemical and ultrastructural characterization of the molecular topography of the rat intestinal microvillous membrane. Assymetric distribution of hydrophilic groups and anionic binding sites. *Gastroenterology* 1983;**85**:46–54.
26 Madara JL. Intestine absorptive cell tight junctions are linked to cytoskeleton. *Am J Physiol* 1987;**253**:C171–5.
27 Madara JL. Loosening tight junctions: lessons from the intestine. *J Clin Invest* 1989;**83**:1089–94.
28 Salzman AL, Wang H, Wollert PS, *et al*. Endotoxin induced ileal mucosal hyperpermeability in pigs; role of tissue acidosis. *Am J Physiol* 1994;**266**:G633–46.
29 Wattanasirichaigoon S, Meconi MJ, Delude RL, Fink MP. Effect of mesenteric ischemia and reperfusion or hemorrhagic shock on intestinal mucosal permeability and ATP content in rats. *Shock* 1999;**12**:127–33.
30 Chiu CJ, McArdle AH, Brown R, Scott HJ, Gurd FN. Intestinal mucosal lesion in low-flow states. *Arch Surg* 1970;**101**:478–83.
31 Fink MP. Gastrointestinal mucosal injury in experimental models of shock, trauma, and sepsis. *Crit Care Med* 1991; **19**:627–41.
32 Sodeyama M, Kirk SJ, Regan MC, Barbul A. The effect of haemorrhagic shock on intestinal amino acid absorption in vivo. *Circ Shock* 1992;**38**:153–6.
33 Takala J. Determinants of splanchnic blood flow. *Br J Anaesth* 1996;**77**:50–8.
34 Kiel JW, Riedel GL, Shepherd AP. Effects of hemodilution on gastric and intestinal oxygenation. *Am J Physiol* 1989;**256**:H171–8.
35 McCord JM. Oxygen-derived free radicals in postischemic tissue injury. *N Engl J Med* 1985;**312**:159–63.
36 Schlag G, Redl H. Mediators of injury and inflammation. *World J Surg* 1996;**20**:406–10.
37 Engler RL, Dahlgren MD, Morris DD, Petersen MA, Schmid-Schönbein GW. Role of leukocytes in response to myocardial ischaemia and reflow in dogs. *Am J Physiol* 1986;**251**:H314–22.
38 Davies MG, Hagen PO. Systemic inflammatory response syndrome. *Br J Surg* 1997;**84**:920–35.
39 Fujishama S, Aikawa N. Neutrophil-mediated tissue injury and its modulation. *Intensive Care Med* 1995;**21**: 277–85.
40 Gawaz M, Fateh-Moghadam S, Pilz G, Gurland HJ, Werdan K. Platelet activation and interaction with leukocytes in patients with sepsis or multiple organ failure. *Eur J Clin Invest* 1995;**25**:843–51.
41 Austen WG Jr, Kyriakides C, Favazza J, Wang Y, Kobzik FD Jr, Hechtman HB. Intestinal ischemia-reperfusion injury is mediated by the membrane attack complex. *Surgery* 1999;**126**:343–8.
42 Spain DA, Fruchterman TM, Matheson PJ, Wilson MA, Martin AW, Garrison RN. Complement activation mediates intestinal injury after resuscitation from hemorrhagic shock. *J Trauma* 1999;**46**:224–33.
43 Dobrina A, Pausa M, Fischetti F, *et al*. Cytologically inactive terminal complement complex causes transendothelial migration of polymorphonuclear leukocytes in vitro and in vivo. *Blood* 2002;**99**:185–92.
44 Wada K, Montalto MC, Stahl GL. Inhibition of complement C5 reduces local and remote organ injury after intestinal ischemia/reperfusion in the rat. *Gastroenterology* 2001;**120**:126–33.
45 Kyriakides C, Austen WG Jr, Wang Y, Favuzza J, Moore FD Jr, Hechtman HB. Neutrophil mediated remote organ injury after lower torso ischemia and reperfusion is selectin and complement dependent. *J Trauma* 2000;**48**: 32–8.
46 Taylor CT, Dzus AL, Colgan SP. Autocrine regulation of epithelial permeability by hypoxia: role for polarized release of tumor necrosis factor alpha. *Gastroenterology* 1998;**114**:657–68.
47 Marcus BC, Wyble CW, Hynes KL, Gewertz BL. Cytokine-induced increases in endothelial permeability occur after adhesion molecule expression. *Surgery* 1996; **120**:411–16.
48 Wright K, Nwariaku F, Halaihel N, Schulman C, Yin HL, Turnage RH. Burn-activated neutrophils and tumor necrosis factor-alpha alter endothelial cell actin cytoskeleton and enhance monolayer permeability. *Surgery* 2000; **128**:259–65.
49 Goldman G, Soffer D, Heller L, Aderka D, Lahat A, Klausner JM. Tumour necrosis factor mediates bacterial translocation after haemorrhagic shock and endotoxaemia. *Eur J Surg* 2001;**167**:299–304.
50 Unno N, Meconi MJ, Smith M, Fink MP. Nitric oxide mediates interferon-gamma-induced hyperpermeability in cultured human intestinal epithelial monolayers. *Crit Care Med* 1995;**23**:1170–6.
51 Sugi K, Musch MW, Field M, Chang EB. Inhibition of Na+, K+-ATPase by interferon gamma down regulates

intestinal epithelial transport and barrier function. *Gastroenterology* 2001;**120**:1393–403.
52 Madara JL, Stafford J. Interferon-γ directly affects barrier function of cultured intestinal epithelial monolayers. *J Clin Invest* 1989;**83**:724–7.
53 Fish SM, Proujansky R, Reenstra WW. Synergistic effects of interferon gamma and tumour necrosis factor alpha on T84 cell function. *Gut* 1999;**45**:191–8.
54 Madsden KL, Lewis SA, Tavernini MM, Hibbard J, Fedorak RN. Interleukin 10 prevents cytokine-induced disruption of T84 monolayer barrier integrity and limits chloride secretion. *Gastroenterology* 1997;**113**:151–9.
55 Colgan SP, Resnick MB, Parkos CA, *et al*. IL-4 directly modulates function of a model human intestinal epithelium. *J Immunol* 1994;**153**:2122–9.
56 Xu D, Lu Q, Deitch EA. Calcium and phospholipase A2 appear to be involved in the pathogenesis of hemorrhagic shock induced mucosal injury and bacterial translocation. *Crit Care Med* 1995;**23**:125.
57 Koike K, Moore EE, Moore FA, Carl VS, Pitman JM, Banerjee A. Phospholipase A_2 inhibition decouples lung injury from gut ischemia reperfusion. *Surgery* 1992;**112**: 173–80.
58 Redl H, Schlag G, Schieber A, Davies J. Tumor necrosis factor is a mediator of phospholipase release during bacteraemia in baboons. *Am J Physiol* 1993;**264**:H2119–23.
59 Anderson BO, Moore EE, Banerjee A. Phospholipase A_2 regulates critical inflammation mediators of multiple organ failure. *Surg Res* 1994;**56**:199–205.
60 Kubes P. Nitric oxide modulates intestinal permeability in the feline small intestine. *Am J Physiol* 1992;**262**:G1138–42.
61 Salzman AL, Menconi MJ, Unno N, *et al*. Nitric oxide dilates tight junctions and depletes ATP in cultured Caco-2Bbe intestinal epithelial monolayers. *Am J Physiol* 1995;**268**:G361–73.
62 Kennedy M, Denenberg AG, Szabo C, Salzman AL. Poly(ADP-ribose) synthetase activation mediates increased permeability induced by peroxynitrite in Caco-2Bbe cells. *Gastroenterology* 1998;**114**:510–18.
63 Smail N, Catania RA, Wang P, Cioffi WG, Bland KI, Chaudry IH. Gut and liver: the organs responsible for increased nitric oxide production after trauma-hemorrhage and resuscitation. *Arch Surg* 1998;**133**:399–405.
64 Mishima S, Xu D, Deitch EA. Increase in endotoxin-induced mucosal permeability is related to increased nitric oxide synthase activity using the Ussing chamber. *Crit Care Med* 1999;**27**:880–6.
65 Kavuklu B, Iskit AB, Guc MO, Ilhan M, Sayek I. Aminoguanidine attenuates endotoxin-induced mesenteric vascular hyporeactivity. *Br J Surg* 2000;**87**:48–53.
66 Suzuki Y, Deitch EA, Mishima S, Lu Q, Xu D. Inducible nitric oxide synthase gene knockout mice have increased resistance to gut injury and bacterial translocation after an intestinal ischaemia-reperfusion injury. *Crit Care Med* 2000;**28**:3692–6.
67 Hernandez G, Velasco N, Wainstein C, *et al*. Gut mucosal atrophy after a short enteral fasting period in critically ill patients. *J Crit Care* 1999;**14**:73–7.
68 Fukuyama K, Iwakiri R, Noda T, *et al*. Apoptosis induced by ischemia-reperfusion and fasting in gastric mucosa compared to small intestinal mucosa in rats. *Dig Dis Sci* 2001;**46**:545–9.
69 Sarac TP, Souba WW, Miller JH, *et al*. Starvation induces differential small bowel luminal amino acid transport. *Surgery* 1994;**116**:679–85.
70 Sharma R, Schumacher U. Morphometric analysis of intestinal mucins under different dietary conditions and gut flora in rats. *Dig Dis Sci* 1995;**40**:2532–9.
71 Deitch E, Winterton J, Li M, Berg R. The gut as a portal of entry for bacteraemia: role of protein malnutrition. *Ann Surg* 1987;**205**:681–92.
72 Juvonen PO, Tenhunen JJ, Heino AA, *et al*. Splanchnic tissue perfusion in acute experimental pancreatitis. *Scand J Gastroenterol* 1999;**34**:308–14.
73 Antonsson J, Boyle C, Kruithoff K, *et al*. Validation of tonometric measurement of gut intramural pH during endotoxaemia and mesenteric occlusion in pigs. *Am J Physiol* 1990;**259**:G519–23.
74 Bonham M, Abu-Zidan F, Simovic M, Windsor J. Gastric intramucosal pH predicts death in severe acute pancreatitis. *Br J Surg* 1997;**84**:1670–4.
75 Wang XD, Wang Q, Andersson R, Ihse I. Alterations in intestinal function in acute pancreatitis in an experimental model. *Br J Surg* 1996;**83**:1537–42.
76 Ryan CM, Schmidt J, Lewandrowski K, *et al*. Gut macromolecular permeability in pancreatitis correlates with severity of disease in rats. *Gastroenterology* 1993; **104**: 890–5.
77 Leeder P RFG K, Davies J, Martin I, McMahon M. Early changes in intestinal permeability seen in patients with severe acute pancreatitis. *Br J Surg* 1997;**84**:696–725.
78 Ammori B, Leeder P, King R, *et al*. Early failure of intestinal barrier function and endotoxaemia in severe pancreatitis. *J Gastrointest Surg* 1999;**3**:252–62.
79 Juvonen PO, Alhava EM, Takala JA. Gut permeability in patients with acute pancreatitis. *Scand J Gastroenterol* 2000;**35**:1314–18.
80 Beger H, Bittner R, Block S, Buchler M. Bacterial contamination of pancreatic necrosis: a prospective clinical study. *Gastroenterology* 1986;**91**:433–41.
81 Cicalese L, Sahai A, Sileri P, *et al*. Acute pancreatitis and bacterial translocation. *Dig Dis Sci* 2001;**46**:1127–32.
82 Nieuwenhuijs VB, Verheem A, van Duijvenbode-Beumer H, *et al*. The role of interdigestive small bowel motility in the regulation of gut microflora, bacterial overgrowth, and bacterial translocation in rats. *Ann Surg* 1998;**228**:188–93.
83 Chen CY, Lu CL, Chang FY, Lu RH, Ng WW, Lee SD.

Endothelin-1 is a candidate mediating intestinal dysmotility in patients with acute pancreatitis. *Dig Dis Sci* 1999; **44**:922–6.

84 Leveau P, Wang X, Soltesz V, Ihse I, Andersson R. Alterations in intestinal motility and microflora in experimental acute pancreatitis. *Int J Pancreatol* 1996; **20**:119–25.

85 Abe R, Shimosegawa T, Moriizumi S, *et al*. Lipoploysaccharide induces manganese superoxide dismutase in the rat pancreas: its role in caerulein pancreatitis. *Biochem Biophs Res Commun* 1995;**217**:1216–22.

86 Kimura K, Shimoseqawa T, Abe R, *et al*. Low doses of lipopolysaccharide upregulate acinar cell apoptosis in caerulein pancreatitis. *Pancreas* 1998;**17**:120–6.

87 Kaiser A, Saluja A, Sengupta A, Saluja M, Steer M. Relationship between severity, necrosis, and apoptosis in five models of experimental acute pancreatitis. *Am J Physiol* 1995;**269**:C1295–C1305.

88 Sandoval D, Gukovskaya A, Reavey P, *et al*. The role of neutrophils and platelet-activating factor in mediating experimental pancreatitis. *Gastroenterology* 1996; **111**: 1081–91.

89 Laine V, Nyman K, Peuravuori H, Henriksen K, Parvinen M, Nevalainen T. Lipopolysaccharide induces apoptosis of rat pancreatic acinar cells. *Gut* 1996;**38**:747–52.

90 Pirisi M, Cavarape A, Fabris C, *et al*. Endotoxin priming exacerbates acute reflex pancreatitis in rats. *Res Exp Med* 1996;**196**:309–15.

91 Pozsar J, Schwab R, Simon K, Fekete L, Orgovan G, Pap A. Effect of endotoxin administration on the severity of acute pancreatitis in two experimental models. *Int J Pancreatol* 1997;**22**:31–7.

92 Wig J, Kochlar R, Ray J, Rao K, Gupta N, Ganguly N. Endotoxaemia predicts outcome in acute pancreatitis. *J Clin Gastroenterol* 1998;**26**:121–4.

93 Windsor J, Feorn K, Ross J, Poxton I, Garden O, Carter D. The role of serum endotoxin and anti-endotoxin core antibody levels in predicting the development of multiple organ failure in acute pancreatitis. *Br J Surg* 1993; **80**: 1042–6.

94 Sautner T, Weesely C, Riegler M, *et al*. Early effects of catecholamine therapy on mucosal integrity, intestinal blood flow and oxygen metabolism in porcine endotoxin shock. *Ann Surg* 1998;**228**:239–48.

95 Denham W, Norman J. The potential role of therapeutic cytokine manipulation in acute pancreatitis. *Surg Clin North Am* 1999;**79**:767–81.

96 Wyncoll DL. The management of severe acute necrotising pancreatitis: An evidence-based review of the literature. *Intensive Care Med* 1999;**25**:146–56.

97 Shader A, JR P. Fatal pancreatitis. *Am J Surg* 1996;**111**: 369–73.

98 McKay CJ, Evans S, Sinclair M, Carter CR, Imrie CW. High early mortality rate from acute pancreatitis in Scotland, 1984–1995. *Br J Surg* 1999;**86**:1302–5.

99 Chiara O, Pelosi P, Segala M, *et al*. Mesenteric and renal oxygen transport during haemorrhage and reperfusion: evaluation of optimal goals for resuscitation. *J Trauma* 2001;**51**:356–62.

100 Santoso JT, Wisner DH, Battistella FD, Owings JT. Comparison of gastric mucosal pH and clinical judgement in critically ill patients. *Eur J Surg* 1998;**164**:521–6.

101 Hamilton MA, Mythen MG. Gastric tonometry: where do we stand? *Curr Opin Crit Care* 2001;**7**:122–7.

102 Miller PR, Meredith JW, Chang MC. Randomized, prospective comparison of increased preload versus inotropes in the resuscitation of trauma patients: effects on cardiopulmonary function and visceral perfusion. *J Trauma* 1998;**44**:107–13.

103 Sims C, Seigne P, Menconi M, *et al*. Skeletal muscle acidosis correlates with severity of blood volume loss during shock and resuscitation. *J Trauma* 2001;**51**:1137–45.

104 Piccoli A, Pittoni G, Facco E, Favaro E, Pillan L. Relationship between central venous pressure and bioimpedence vector analysis in critically ill patients. *Crit Care Med* 2000;**28**:132–7.

105 Farco J, Raffey P, Zellman V, Katz RL. Intraoperative evaluation of tissue perfusion in high risk patients and non-invasive hemodynamic monitoring. *Crit Care Med* 1999;**27**:2298–9.

106 Knol J, Inman M, Strodel W, Eckhauser F. Pancreatic response to crystalloid resuscitation in experimental pancreatitis. *J Surg Res* 1987;**43**:387–92.

107 Koustova E, Gushchin V, Stanton K, *et al*. Lactated Ringer's revisited: gene expression profiling of fluid-stimulated human leukocytes. *J Trauma* 2001;**51**:205.

108 Sims CA, Wattanasirichaigoon S, Menconi MJ, Ajami AM, Fink MP. Ringer's ethyl pyruvate solution ameliorates ischaemia/reperfusion-induced intestinal mucosal injury in rats. *Crit Care Med* 2001;**29**:1636–7.

109 Guschchin V, Stegalkina S, Alam H, *et al*. Is hypertonic saline really immunosuppressive? Genes tell a different story. *J Trauma* 2001;**51**:211.

110 Junger WG, Coimbra R, Liu FC, *et al*. *Shock* 1997;**8**:235–41.

111 Shields CJ, Winter DC, Sookhai S, Ryan L, Kirwan WO, Redmond HP. *Br J Surg* 2000;**87**:1336–40.

112 Yada-Langui MM, Coimbra R, Lancellotti C, *et al*. Hypertonic saline and pentoxifylline prevent lung injury and bacterial translocation after haemorrhagic shock. *Shock* 2000;**14**:594–8.

113 Huang PP, Stucky FS, Dimick AR, Treat RC, Bessey PQ, Rue LW. Hypertonic sodium resuscitation is associated with renal failure and death. *Ann Surg* 1995;**221**:543–54.

114 Klar E, Herfarth C, Messmer K. Therapeutic effect of isovolemic hemodilution with dextran 60 on the impair-

ment of pancreatic microcirculation in acute biliary pancreatitis. *Ann Surg* 1990;**211**:346–53.
115 Klar E, Foitzik T, Buhr H, Messmer K, Herfarth C. Isovolaemic hemodilution with dextran 60 as treatment of pancreatic ischemia in acute pancreatitis. Clinical practicability of an experimental concept. *Ann Surg* 1993;**217**: 369–74.
116 Mortier E, Ongenae M, DeBaerdemaeker L, *et al*. In vitro evaluation of the effect of profound haemodilution with hydroxyethyl starch 6%, modified fluid gelatin 4%, and dextran 40 10% on coagulation profile measured by thromboelastography. *Anaesthesia* 1997;**52**:1061–4.
117 Bapot PP, Raine GJ. Use of dextran-70 for fluid resuscitation has been dying out. *Br Med J* 1998;**317**:277.
118 Von Dobscheutz E, Hoffmann T, Messmer K. Diaspirin cross-linked hemoglobin effectively restores pancreatic microcirculatory failure in hemorrhagic shock. *Anesthesiology* 1999;**91**:1754–62.
119 Sielenkamper AW, Eichelbronner O, Martin CM, Madorin SW, Chin-Yee IH, Sibbald WJ. Diaspirin cross-linked hemoglobin improves mucosal perfusion in the ileum of septic rats. *Crit Care Med* 2000;**28**:782–7.
120 Johnson JL, Moore EE, Offner PJ, *et al*. Resuscitation with a blood substitute abrogates pathologic postinjury neutrophil cytotoxic function. *J Trauma* 2001;**50**:449–55.
121 Saxena R, Wijnhoud AD, Carton H, *et al*. Controlled safety study of a hemoglobin-based oxygen carrier, DCLHb, in acute ischemic stroke. *Stroke* 1999;**31**:546–8.
122 Sloan EP, Koenigsberg M, Gens D, *et al*. Diaspirin cross-linked hemoglobin (DCLHb) in the treatment of severe traumatic haemorrhagic shock: a randomised controlled efficacy trial. *JAMA* 1999;**282**:1857–64.
123 Gould SA, Moore EE, Hoyt DB, *et al*. The life-saving capacity of human polymerised hemoglobin in massive blood loss when blood may be unavailable. *Am Coll Surg Clin Congress Paper Session* 2001.
124 Balogh Z, Wolford A, Szalay L, *et al*. Sodium dalteparin treatment during resuscitation inhibits hemorrhagic shock induced leukocyte rolling and adhesion in the mesenteric microcirculation. *J Trauma* 2001;**51**:199.
125 Kincaid E, Miller P, Meredith J, Chang M. Enalapril improves gut perfusion in critically injured patients. *Shock* 1998;**9**:79–83.
126 Kuebler JF, Jarrar D, Toth B, *et al*. Estradiol administration improves splanchnic perfusion following trauma-haemorrhage and sepsis. *Arch Surg* 2002;**137**:74–9.
127 Sautner T, Wessely C, Riegler M, *et al*. Early effects of catecholamine therapy on mucosal integrity, intestinal blood flow, and oxygen metabolism in porcine endotoxin shock. *Ann Surg* 1998;**228**:239–48.
128 Ruokonen E, Uusaro A, Alhava E, Takala J. The effect of dobutamine infusion on splanchnic blood flow and oxygen transport in patients with acute pancreatitis. *Intensive Care Med* 1997;**23**:732–7.
129 Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *JAMA* 1994; **272**:1354–7.
130 Meier-Hellman A, Bredle DL, Specht M, Spies C, Hannemann L, Reinhart K. The effects of low-dose dopamine on splanchnic blood flow and oxygen uptake in patients with septic shock. *Intensive Care Med* 1997;**23**: 31–7.
131 Smithies M, Yee TH, Jackson L, Beale R, Bihari D. Protecting the gut and the liver in the critically ill: effects of dopexamine. *Crit Care Med* 1994;**22**:789–95.
132 Schmidt H, Secchi A, Wellmann R, Bach A, Bhrer H, Martin E. Dopexamine maintains intestinal villus blood flow during endotoxaemia in rats. *Crit Care Med* 1996;**24**: 1233–7.
133 Kiefer P, Tugtekin I, Wiedeck H, *et al*. Effect of dopexamine-induced increase in cardiac index on splanchnic hemodynamics in septic shock. *Am J Respir Crit Care Med* 2000;**161**:775–9.
134 Klar E, Rattner D, Compton C, Stanford G, Chernow B, Warshaw A. Adverse effect of therapeutic vasoconstrictors in experimental pancreatitis. *Ann Surg* 1991;**214**:186–74.
135 Karanjia ND, Widdison AL, Lutrin FJ, Chang YB, Reber HA. The antiinflammatory effect of dopamine in alcoholic hemorrhagic pancreatitis in cats. Studies on the receptors and mechanisms of action. *Gastroenterology* 1991;**101**:1635–41.
136 Windsor J, Hammodat H. The metabolic management of acute pancreatitis. *World J Surg* 2000;**24**:664–72.
137 Latifi R, McIntosh JK, Dudrick SJ. Nutritional management of acute and chronic pancreatitis. *Surg Clin North Am* 1991;**71**:579–95.
138 Vison N, Hecketsweiler P, Butel J, Bernier J. Effect of continuous jejunal perfusion of elemental and complex nutritional solutions on pancreatic enzyme secretion in human subjects. *Gut* 1978;**19**:194–8.
139 Abou-Assi S, Okeefe SJ. Nutrition in acute pancreatitis. *J Clin Gastroenterol* 2001;**32**:203–9.
140 Alverdy J, Aoys E, Moss G. Total parenteral nutrition promotes bacterial translocation from the gut. *Surgery* 1988;**104**:185–90.
141 King BK, Kudsk KA. A temporal study of TPN-induced changes in gut-associated lymphoid tissue and mucosal immunity. *Arch Surg* 1997;**132**:1303–9.
142 Saito H, Trocki O, Alexander J, Kopcha R, Heyd T, Joffe S. The effect of route of nutrient administration on the nutritional state, catabolic hormone secretion and gut mucosal integrity after burn injury. *J Parenteral Enter Nutr* 1987;**11**:1–7.
143 Illig K, Ryan C, Hardry D, Rhodes J, Locke W, Sax H. Total parenteral nutrition induced changes in gut

mucosal function: atrophy alone is not the issue. *Surgery* 1992;**112**:631–7.
144 Kotani J, Usami M, Nomura H, *et al*. Enteral nutrition prevents bacterial translocation but does not improve survival during pancreatitis. *Arch Surg* 1999;**134**:287–92.
145 Windsor AC, Kanwar S, Li AG, *et al*. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut* 1008;**42**:431–5.
146 Kalfarentzos F, Kehagias J, Mead N, Kokkinis K, Gogos CA. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomised prospective trial. *Br J Surg* 1997;**84**:1665–9.
147 McClave S, Snider H, Owens N, Sexton L. Clinical nutrition in pancreatitis. *Dig Dis Sci* 1997;**42**:2035–44.
148 Beale RJ, Bryg DJ, Bihari DJ. Immunonutrition in the critically ill: a systematic review of clinical outcome. *Crit Care Med* 1999;**27**:2799–805.
149 Schneider H, Boyle N, McCluckie A, Beal R, Atkinson S. Acute severe pancreatitis and multiple organ failure: total parenteral nutrition is still required in a proportion of patients. *Br J Surg* 2000;**87**:362–73.
150 Omura K, Hirano K, Kanehira E, *et al*. Small amount of low-residue diet with parenteral nutrition can prevent decreases in intestinal mucosal integrity. *Ann Surg* 2000; **231**:112–18.
151 Gloor B, Muller CA, Worni M, Martignoni ME, Uhl W, Buchler MW. Late mortality in patients with severe acute pancreatitis. *Br J Surg* 2001;**88**:975–9.
152 Chen X, Valente J, Alexander J. The effect of sennosides on bacterial translocation and survival in a model of acute haemorrhagic pancreatitis. *Pancreas* 1999;**18**:39–46.
153 Marotta F, Geng T, Wu C, Barbi G. Bacterial translocation in the course of acute pancreatitis: beneficial role of nonabsorbable antibiotics and lactidiol enemas. *Digestion* 1996;**57**:446–52.
154 Gianotti L, Munda R, Gennari R, Pyles T, Alexander J. Effect of different regimens of gut decontamination on bacterial translocation and mortality in experimental acute pancreatitis. *Eur J Surg* 1995;**161**:85–92.
155 Mithofer K, Fernandez-del Castillo C, Ferraro M, Lewandrowski K, Rattner D, Warshaw A. Antibiotic treatment improves survival in experimental acute necrotizing pancreatitis. *Gastroenterology* 1996;**110**:232–40.
156 Foitzik T, Fernandez-del Castillo C, Ferrarro MJ, Mithofer K, Rattner DW, Warshaw Al. Pathogenesis and prevention of early pancreatic infection in experimental acute necrotizing pancreatitis. *Ann Surg* 1995;**222**:179–85.
157 Powell J, Miles R, Siriwardena A. Antibiotic prophylaxis in the initial management of severe acute pancreatitis. *Br J Surg* 1998;**85**:582–7.
158 Delcenserie R, Yzet T, Ducroix JP. Prophylactic antibiotics in treatment of severe acute alcohol pancreatitis. *Pancreas* 1996;**13**:198–201.
159 Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomised multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. *Surg Gynecol Obstet* 1993;**176**: 480–3.
160 Sainio V, Kemppainen E, Puolakkainen P, *et al*. Early antibiotic treatment in acute necrotizing pancreatitis. *Lancet* 1995;**346**:663–7.
161 Luiten EJ, Hop WC, Lange JF, Bruining HA. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. *Ann Surg* 1995;**222**:57–65.
162 Golub R, Siddiqi F, Pohl D. Role of antibiotics in acute pancreatitis: a meta-analysis. *J Gastrointest Surg* 1998;**2**: 496–503.
163 Sharma VK, Howden CW. Prophylactic antibiotic administration reduces sepsis and mortality in acute necrotizing pancreatitis: a meta-analysis. *Pancreas* 2001; **22**:28–31.
164 Bassi C, Falconi M, Talamini G, *et al*. Controlled clinical trial of perfloxacin versus imipenem in severe acute pancreatitis. *Gastroenterology* 1998;**115**:1513–17.
165 Nordback I, Sand J, Saaristo R, Paajanen H. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis – a single-center randomised study. *J Gastrointest Surg* 2001;**5**:113–20.
166 Baron T, Morgan D. Acute necrotizing pancreatitis. *N Engl J Med* 1999;**340**:1412–17.
167 Gloor B, Muller CA, Worni M, *et al*. Pancreatic infection in severe pancreatitis: the role of fungus and multiresistant organisms. *Arch Surg* 2001;**136**:592–6.
168 Norman J. The role of cytokines in the pathogenesis of acute pancreatitis. *Am J Surg* 1998;**175**:76–83.
169 Abu-Zidan FM, Windsor JA. Lexipafant and acute pancreatitis: a critical appraisal. *Eur J Surg* 2002; **168**: 215–19.
170 Simovic M, Bonham M, Abu-Zidan F, Windsor J. The anti-inflammatory cytokine response and clinical outcome in severe acute pancreatitis. *Crit Care Med* 1999; **27**: 2662–5.
171 Bonham M, Winterbourn C, Windsor J. Lipid peroxidation in acute pancreatitis. *Aust NZ J Surg* 1996;**66**:238.
172 Simovic M, Bonham M, Abu-Zidan F, Windsor J. Manganese superoxide dismutase: a marker of ischaemia reperfusion injury in acute pancreatitis? *Pancreas* 1997;**14**: 78–82.
173 Bonham M, Abu-Zidan FM, Simovic MO, *et al*. Early ascorbic acid depletion is related to the severity of acute pancreatitis. *Br J Surg* 1999;**86**:1296–301.
174 Abu-Zidan F, Bonham M, Windsor J. The severity of acute pancreatitis: a multivariate analysis of oxidative

stress markers and the modified Glasgow criteria. *Br J Surg* 2000;**87**:1019–23.
175 Spark J, Chetter I, Gallavin L, Kester R, Guillou P, Scott D. Reduced total antioxidant capacity predicts ischaemia-reperfusion injury after femordistal bypass. *Br J Surg* 1998; **85**:221–5.
176 Demols A, Van Laethem JL, Quertinmony E, *et al*. N-acetylcysteine decreases the severity of acute pancreatitis in mice. *Pancreas* 2000;**20**:161–9.
177 Qi W, Tan DX, Reiter RJ, *et al*. Melatonin reduces lipid peroxidation and tissue edema in caerulein-induced acute pancreatitis in rats. *Dig Dis Sci* 1999;**44**:2257–62.
178 Schulz HU, Hoenl H, Schrader T, *et al*. Randomized, placebo-controlled trial of lazaroid effects on severe acute pancreatitis in rats. *Crit Care Med* 2001;**29**:861–9.
179 Ahn BO, Kim KH, Lee G, *et al*. Effects of taurine on caerulein-induced acute pancreatitis in the rat. *Pharmacology* 2001;**63**:1–7.
180 Barquist E, Kirton O, Windsor J, *et al*. The impact of antioxidant and splanchnic-directed therapy on persistent uncorrected gastric mucosal pH in the critically injured trauma patient. *J Trauma Inj Inf Crit Care* 1998;**44**:355–60.
181 Kirton O, Civetta J, Hudson-Civetta J, *et al*. Gastric mucosal pH (pHi) driven resuscitation and antioxidants: normalized pHi associated with high survival. *Crit Care Med* 1998;**26 (Suppl)**:377.
182 Denham W, Norman J. The potential role of therapeutic cytokine manipulation in acute pancreatitis. *Surg Clin North Am* 1999;**79**:767–81.
183 Abraham E, Wunderink R, Silverman H, *et al*. Efficacy and safety of monoclonal antibody to human tumor necrosis factor alpha in patients with sepsis syndrome: a randomised, controlled, double blinded multicentric clinical trial. *JAMA* 1995;**273**:934–41.
184 Fisher CJ, Dhainaut J-FA, Opal SM, *et al*. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. *JAMA* 1994;**271**:1836–43.
185 O'Keefe GE, Peters D, Munford RS, *et al*. The G→ a single nucleotide pleomorphism (SNP) at the –308 position in the TNF-α promotor increases the risk for severe sepsis after trauma. *J Trauma* 2001;**51**:204.
186 Hughes C, Grewal H, Gaber L, *et al*. Anti-TNFα therapy improves survival and ameliorates the pathophysiologic sequelae in acute pancreatitis in the rat. *Am J Surg* 1996; **171**:274–80.
187 Windsor A, Mullen P, Walsh C, *et al*. Delayed tumour necrosis factor alpha blockade attenuates pulmonary dysfunction and metabolic acidosis associated with experimental gram negative sepsis. *Arch Surg* 1994;**129**:80–9.
188 Tanaka N, Murata A, Uda K, *et al*. Interleukin-1 receptor antagonism modifies the changes in vital organs induced by acute necrotizing pancreatitis in a rat experimental model. *Crit Care Med* 1995;**23**:901–8.
189 Rongione A, Kusske A, Ashley S, Reber H, McFadden D. Interleukin-10 reduces the severity of acute pancreatitis in the rat. *Gastroenterology* 1995;**112**:960–7.
190 Kusske A, Rongiode A, Ashley S, McFadden D, Reber H. Interleukin 10 prevents death in lethal necrotizing pancreatitis in mice. *Surgery* 1996;**120**:284–8.
191 Denham W, Denham D, Yang J, *et al*. Transient human gene therapy: a novel cytokine regulatory strategy for experimental pancreatitis. *Ann Surg* 1998;**227**:812–20.
192 Deviere J, Le Moine O, Van Laethem JL, *et al*. Interleukin 10 reduces the incidence of pancreatitis after therapeutic endoscopic retrograde cholangiopancreatography. *Gastroenterology* 2001;**120**:498–505.
193 Dumot JA, Conwell DL, Zuccaro G Jr *et al*. A randomised, double blind study of interleukin 10 for the prevention of ERCP-induced pancreatitis. *Am J Gastroenterol* 2001;**96**: 2098–102.
194 Tan X, Wang H, Gonzalez-Crussi F, Chang H, Hsueh W. Platelet-activating factor and endotoxin increase the enzyme activity and gene expression of type II phospholipase A2 in the rat intestine: role of polymorphonuclear leukocytes. *J Immunol* 1996;**156**:2985–90.
195 Andersson R, Wang X, Sun Z, Deng X, Soltesz V, Ihse I. Effect of a platelet-activating factor antagonist on pancreatitis-associated gut barrier dysfunction in rats. *Pancreas* 1998;**17**:107–19.
196 Liu O, Djuricin G, Rossi H, *et al*. The effect of lexipafant on bacterial translocation in acute necrotizing pancreatitis in rats. *Am Surg* 1999;**65**:611–17.
197 Yamaguchi Y, Matsumura F, Liang J, *et al*. Platelet-activating factor antagonist (TCV-309) attenuates the priming effects of bronchoalveolar macrophages in cerulein-induced pancreatitis rats. *Pancreas* 1999; **18**: 355–63.
198 Dabrowski A, Gabryelewicz A, Chyczewski L. The effect of platelet activating factor antagonist (BN52021) on acute experimental pancreatitis with reference to multi-organ oxidative stress. *Int J Pancreatol* 1995;**17**:173–80.
199 Poeze M, Froon AH, Ramsay G, Buurman WA, Greve JW. Decreased organ failure in patients with SIRS and septic shock treated with the platelet-activating factor antagonist TCV-309: a prospective, multicenter, double-blind, randomised phase II trial. TCV-309 Septic Shock Study Group. *Shock* 2000;**14**:421–8.
200 Johnson CD, Kingsnorth AN, Imrie CW, *et al*. Double blind, randomised, placebo controlled study of a platelet activating factor antagonist, lexipafant, in the treatment and prevention of organ failure in predicted severe acute pancreatitis. *Gut* 2001;**48**:62–9.
201 Wang X, Sun Z, Borjesson A, Andersson R. Inhibition of platelet-activating factor, intercellular adhesion molecule 1 and platelet cellular adhesion molecule 1 reduces ex-

perimental pancreatitis-associated gut endothelial barrier dysfunction. *Br J Surg* 1999;**86**:411–16.
202 Lundberg AH, Fukatsu K, Gaber L, *et al*. Blocking pulmonary ICAM-1 expression ameliorates lung injury in established diet-induced pancreatitis. *Ann Surg* 2001;**233**: 213–20.
203 Werner L, Z'graggen K, Dernandez-del Castillo C, Lewandrowski KB, Compton CC, Warshaw AL. Specific therapy for local and systemic complications of acute pancreatitis with monoclonal antibodies against ICAM-1. *Ann Surg* 1999;**229**:834–40.
204 Yamaguchi Y, Okabe K, Liang J, *et al*. The novel carboxamide derivative IS-741 reduces neutrophil chemoattractant production by bronchoalveolar macrophages in rats with cerulein-induced pancreatitis complicated by sepsis. *Digestion* 1999;**60 Suppl 1**:52–6.
205 Bhatia M, Brady M, Zagorski J, *et al*. Treatment with neutralising antibody against cytokine induced neutrophil chemoattractant (CINC) protects against acute pancreatitis associated lung injury. *Gut* 2000;**47**:838–44.
206 Marik PE. Gastric mucosal pH: a better predictor of multiorgan dysfunction syndrome and death than oxygen derived variables in patients with sepsis. *Chest* 1993;**104**: 225–9.
207 Ivatury RR, Simon RJ, Havriliak D, Garcia C, Greenbarg J, Stahl WM. Gastric mucosal pH and oxygen delivery and oxygen consumption indices in the assessment of adequacy of resuscitation after trauma: a prospective, randomised study. *J Trauma Inj Inf Crit Care* 1995;**39**: 128–36.
208 Vincent J. Gastric mucosal pH is definitely obsolete – please tell us more about gastric mucosal pCO_2. *Crit Care Med* 1998;**26**:1479–81.
209 Murray M, Gonze M, Nowak L, Cobb C. Serum D-lactate levels are an aid to diagnosing acute intestinal ischaemia. *Am J Surg* 1994;**167**:575–8.
210 Lieberman J, Marks W, Cohn S, *et al*. Organ failure, infection and the systemic inflammatory response syndrome are associated with elevated levels of urinary fatty acid binding protein: study of 100 consecutive patients in a surgical intensive care unit. *J Trauma Inj Inf Crit Care* 1998;**45**:900–6.
211 Rahman SH, James AM, Ammori BJ, Larvin M, McMahon MJ. Ischaemia-reperfusion injury contributes to increased permeability in severe acute pancreatitis. *Turning Science into Medicine; Digestive Disease Week* 2002: A590.
212 Ammori BJ, Becker KL, Kite P, *et al*. Calcitonin precursors (CTpr): early markers of gut barrier dysfunction in patients with acute pancreatitis. *Br J Surg* 2002;**89**:S29.
213 Wilmore D. Polymerase chain reaction surveillance of microbial DNA in critically ill patients: exploring another frontier. *Ann Surg* 1998;**227**:10–11.

English or American?

For the first four volumes of *HPB* the Editor has 'translated' all papers into British English in order to achieve uniformity of style. However, as this is an international journal the Editorial Board has decided that from now on manuscripts may be written in either British English or American English as long as usage is consistent throughout the paper.

It is a requirement that laboratory values should be given in SI (Standard International) units. However, if authors so wish American units can be given as well in brackets, e.g. bilirubin 35.9 μmol/L (2.1 mg/dl).

Robin Williamson
Editor