The Gut-Liver Axis in Multiple Organ Failure

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Introduction

Advances in the management of acute life-threatening illness have resulted in progressively improving rates of survival for a broad spectrum of disorders. These same advances, directed against the immediate threat to survival posed, for example, by bleeding, infection, or acute organ system failure, have profoundly altered patterns of morbidity and mortality in critical illness. In the wake of increasing success in the management of acute physiological instability has arisen a new series of clinical challenges: those that result not from the original injury but from the host response to injury, and from the therapeutic measures taken to achieve short term survival.

Rapid resuscitation, timely transport, and aggressive surgical intervention following multiple trauma, for example, effected a reduction in immediate mortality related to hemorrhagic shock, but simultaneously set the stage for the emergence of a new post-resuscitation syndrome: the adult respiratory distress syndrome (ARDS); support of the lung by mechanical ventilation, in turn, created a new series of problems including barotrauma and ventilator-associated pneumonia. The development of total parenteral nutrition has permitted prolonged survival in the absence of oral intake, but at the cost of TPN-induced cholestasis and liver dysfunction. The early control of life-threatening infections by physiological support and potent antimicrobial agents was a necessary prelude to the emergence of superinfection with organisms such as coagulase-negative *Staphylococci* and *Candida*. These new clinical challenges, arising in the wake of the treatment of a primary life-threatening disorder, comprise the post-resuscitation syndrome known variously as multiple organ failure (MOF) or multiple organ dysfunction syndrome (MODS), now the leading cause of ICU mortality [1].

MOF is best conceptualized as a syndrome of altered homeostasis which develops in the wake of a life-threatening insult, and which arises as a result of the *response* to the original insult or its treatment. The syndrome is intimately related to infection and the host septic response, mediated in turn by products of host immune cells- cytokines, prostanoids, and intermediates of oxygen and nitrogen. These mediators can produce both organ injury and an acquired state of immune dysfunction which, in concert with the influences

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of invasive monitoring devices and broad spectrum antibiotics, predisposes to the development of superinfection, and perpetuation of the syndrome.

This paradigm, injury resulting from the response to prior injury, defines the syndrome of MOF and establishes a conceptual framework for the present review of the gut-liver axis as a potential second insult in the pathogenesis of MOF, and in particular, in the pathogenesis of the state of altered immune homeostasis which characterizes the syndrome.

The Gut in Critical Illness: An Historical Perspective

The concept that the gastrointestinal (GI) tract is central to the systemic derangements associated with acute illness can be traced back four millennia. The Egyptians believed that a toxic factor of intestinal origin, designated as WHDW (and pronounced 'ukhedu'), could pass into the body producing illness or death [2]. Similar ideas were propounded by the Greeks, and the word 'sepsis' as used by Hippocrates and Aristotle denoted a process of putrefaction occurring within the colon and differentiated from the companion process of 'pepsis' or digestion [3].

Metchnikoff, at the turn of this century, proposed that a spectrum of problems ranging from puerperal fever to premature senility arose as a consequence of the absorption of toxins produced by the intestinal flora [4]. His concepts led to the popular belief that dietary supplementation with yogurt could promote longevity by modifying gut flora and stimlated a brief period of enthusiasm for even more drastic measures. The British surgeon, Sir Arbuthnot Lane, advocated colectomy as the treatment for chronic intestinal stasis [5], a practise lampooned in Shaw's play *A Doctor's Dilemma*.

Studies by Fine and others, beginning around 1950, demonstrated that bacteria could pass from the intestine into the peritoneal cavity in the setting of a sterile chemical peritonitis [6], and implicated a factor of intestinal origin in the lethality associated with hemorrhagic shock [7, 8]. This factor proved to be gram-negative bacterial endotoxin [9]. It was shown, moreover, that not only was the gut a source of endotoxin, it also contributed to the lethality of endotoxemia, since a 90% enterectomy significantly improved rates of survival following endotoxin infusion in a canine model [10]. The concept that the gut can amplify injury in critical illness thus dates back a quarter of a century.

Contemporary interest in the gut in critical illness stems from a series of observations regarding infection in the critically ill. ICU-acquired infections often develop in the absence of a well-defined reservoir of the causative organisms, and involve a microbial spectrum which is fundamentally different from the flora of community-acquired infections [11–13]. Control of infection does not necessarily result in diminution of the associated septic response or in a reduction in mortality [14, 15]. The MOF syndrome classically arises in patients with uncontrolled intraabdominal infection in whom the in-

fectious focus lies immediately adjacent to the GI tract [16], yet control of that infection frequently fails to reverse organ failure [17].

We and others have hypothesized that interactions between the GI tract and the liver contribute to the evolution and expression of the MOF syndrome [18–21]. Briefly sketched, the gut hypothesis proposes in alternate mechanism for the initiation and perpetuation of the host septic response. Critical illness and its management alters normal patterns of proximal GI colonization with the result that the gut becomes overgrown with common ICU pathogens. These organisms can enter the host and produce foci of invasive ICU-acquired infection either by aspiration of contaminated gastric secretions or by translocation across an altered mucosal barrier. Additionally, however, interactions between microorganisms or their products and immune cells in the gut mucosa and liver may trigger the local release of the biochemical mediators of the septic response. The resultant mediator cascade, initiated within the gut mucosa or liver becomes manifest as a systemic syndrome of clinical sepsis and its ultimate consequence, organ dysfunction, in the absence of demonstrable invasive infection.

Altered Proximal GI Flora in Critical Illness

In health, the proximal GI tract is sterile or lightly colonized with gram-positive organisms and *Lactobacilli* [22]. Hypochlorhydria, as a consequence of medical [23] or surgical [24] vagotomy or in conjunction with pernicious anemia [25], is associated with significant overgrowth by gram-negative organisms. Small bowel overgrowth with gram-negatives is also evident in the patient with liver disease [26, 27].

Colonization of the upper GI tract develops rapidly following admission to an ICU [28, 29]. Its causes are multifactorial. Human studies have shown that the use of acid-reducing measures for the prophylaxis of stress ulceration predisposes to gram-negative bacterial overgrowth [30, 31], however since gram-positive organisms and fungi are also found in increased numbers, other causes are likely. In animal models, peritonitis [32], interruption of bile flow [33], and disruption of the normal microbial ecology with broad spectrum antibiotics [34, 35] all produce gut microbial overgrowth.

In a study of 34 critically ill patients admitted to a surgical ICU, we found *Candida, Pseudomonas, S. epidermidis*, and the enterococcus to be the most common species colonizing the upper GI tract, with mean concentrations ranging from 10^4 to 10^7 CFU/ml of GI fluid [36]. Gut colonization was significantly associated with the development of invasive infection with *Candida, Pseudomonas*, and *S. epidermidis*; these infections included not only pneumonia, but also recurrent peritonitis, urinary tract infections, and bacteremias.

Interactions between Gut Flora and the Host

The relationship between the indigenous GI flora and the normal host is a symbiotic one: the host provides nutrients and optimal conditions for microbial growth, the organism, in turn, exerts multiple beneficial influences on systemic homeostasis. Studies in germfree animals, for example, have shown that an intact microbial flora is a prerequisite for normal morphologic development of the small bowel and an important factor in the regulation of the rate of intestinal transit [37].

The indigenous intestinal flora plays a critical role in normal immunologic development. The spleen of the germfree animal contains fewer T helper cells [38], and unlike their conventional counterparts, these animals fail to develop normal delayed type hypersensitivity responses following immunization with sheep red blood cells [39]. Neutrophils [40] and macrophages [41] from the germfree animal display impaired chemotaxis in response to an inflammatory stimulus. Germfree animals are highly susceptible to infection with *S. aureus* or *Klebsiella*, yet resistant to doses of endotoxin which are lethal to conventional animals [42]. Gram-negative colonization of the GI tract has also been shown to regulate macrophage-mediated suppression of the secondary antibody response [43].

The indigenous gastrointestinal flora has been implicated in a diverse group of diseases which share, as a common feature, abnormalities in immune regulation. Experimental liver injury resulting from either dietary deficiency of choline [44] or administration of carbon tetrachloride [45] can be minimized by antimicrobial therapy directed against intestinal gram-negative aerobes, and in particular, by neutralization of gut endotoxin. Similarly, the liver injury resulting following infection with Frog Virus 3 is largely prevented by prior colectomy [46]. Autoimmune thyroiditis in susceptible animals is attenuated by oral antibiotics; restoration of the normal gram-negative flora results in exacerbation of the thyroiditis [47]. Intestinal bacterial products also appear to play a role in the pathogenesis of experimental arthritis [48, 49].

Profound dysregulation of normal immunologic responsiveness is a prominent feature of MOF [50]; changes in the gut flora potentially contribute to this state by one of four mechanisms:

1. aspiration of contaminated upper GI fluids resulting in pneumonia and its sequelae;
2. translocation of viable microorganisms across the gut mucosa producing invasive infection with its sequelae;
3. absorption of endotoxin into the portal vein resulting in the release of mediator molecules from Kupffer cells and hepatocytes, and
4. local activation of immunologically competent cells in the gut mucosa with the release of regulatory mediators into the mesenteric lymphatics or portal vein.

Aspiration Pneumonitis and its Sequelae

Subclinical aspiration of colonized gastric secretions is an important cause of pneumonia in the intubated ICU patient [30, 31, 51, 52]. Aspirated microorganisms can proliferate in the lung, producing local tissue injury, or spread hematogenously or via lymphatics to other sites in the body. They also interact with local host phagocytic cells, predominantly alveolar macrophages and neutrophils, and the biochemical products of these interactions in turn can induce local and distant tissue injury.

Alveolar macrophages release tumor necrosis factor (TNF) and interleukin-1 (IL-1) in response to bacterial endotoxin stimulation both *in vivo* [53] and *in vitro* [54]; in fact, LPS-triggered alveolar macrophages release substantially more TNF than Kupffer cells do [55]. Endotoxin also stimulates alveolar macrophages to release a potent neutrophil chemo-attractant (likely the cytokine IL-8), resulting in augmented accumulation of neutrophils in the alveoli [56, 57]. Both TNF [58] and neutrophil products [59] induce the characteristic lung injury of ARDS in the experimental animal.

Alveolar macrophages also exert an important immunoregulatory influence *in vivo*, downregulating the response of lymphocytes to activation by antigen or mitogen [60, 61].

Bacterial Translocation

Extensive studies both in animals [62–65] and humans [66–68] have shown that bacterial translocation, the passage of intact, viable bacteria through the GI tract into sterile host tissues, is a common phenomenon when normal physiological homeostasis is disrupted. The factors promoting translocation in the experimental animal (shock, trauma, hemorrhage, malnutrition, absence of enteral feeding, endotoxemia, and obstructive jaundice), are factors which are commonly present in the critically ill patient [69]. Moreover, translocating bacterial species include all of the common isolates from ICU-acquired infections: *Pseudomonas* [70], *Candida* [66], coagulase-negative *Staphylococci* and the enterococcus [64].

It is well-established that bacterial translocation occurs; it is less clear whether it is a mechanism of disease or an epiphenomenon. Transient bacteremia can be detected in patients undergoing sigmoidoscopy [71] or colonoscopy [72] in the absence of obvious systemic sequelae; on the other hand, translocation of *Candida* by oral ingestion of a large fungal inoculum by a healthy human volunteer resulted in significant systemic upset [66]. Disruption of the normal GI flora, particularly the anaerobic flora, can cause bacterial translocation. Translocation induced by gut overgrowth with *E. coli* is associated with suppression of lymphocyte proliferation *in vitro* [73] and of delayed hypersensitivity responsiveness *in vivo* [74] as well as with augmentation of Kupffer cell procoagulant activity

[75]. On the other hand, suppression of gut flora by oral non-absorbed antibiotics does not improve outcome in experimental models of burn wound infection [76] or zymosan peritonitis [77], despite a reduction in rates of bacterialtranslocation.

Absorption of Endotoxin

Bacteria identified by culture of host tissues represent only a very small proportion of the body burden of bacteria or bacterial products present in models of bacterial translocation, since nonviable organisms outnumber viable organisms by a factor of as much as one hundred to one [78]. The physiological effects seen in association with bacterial translocation may, therefore, be a consequence of the absorption of endotoxin, rather than the translocation of live organisms.

Despite the presence of large amounts of endotoxin within the gut lumen, the normal gut mucosa forms an effective barrier, and systemic absorption of endotoxin is minimal [79]. Increased passage of endotoxin across the gut mucosa occurs under circumstances similar to those which facilitate bacterial translocation. Absorption of endotoxin has been documented in experimental models following surgery [80] and hemorrhagic shock [81], and in the presence of small bowel obstruction [82]. Systemic endotoxemia, presumably of gut origin, can be demonstrated in human burn victims [83] and in patients with inflammatory bowel disease [84]. The portal vein appears to be the most important route of uptake of endotoxin absorbed from the GI tract [85]. Concentrations of endotoxin in the portal blood are elevated following cecal perforation [85] and small bowel obstruction [82] in experimental animals. Few data are available regarding portal endotoxemia in humans. Low level portal endotoxemia has been detected in otherwise healthy humans undergoing laparotomy [86] and in patients with liver disease [87]. On the other hand, endotoxin was not found in portal blood in the first five days following abdominal trauma [88], nor in patients who do not have concomitant GI disease [89]. It is probable that if portal endotoxemia occurs normally, it does so intermittently or at only very low concentrations.

Local Activation of Gut Associated Lymphoid Tissues

The GI tract is a complex immunoregulatory organ which has evolved to serve a dual role: the exclusion of potentially harmful microorganisms from the environment and the downregulation of injurious immune reactions to ingested foodstuffs. Gut associated lymphoid tissues (GALT) are found throughout the length of the GI tract and include lymphocytes, mast cells, macrophages, and specialized sampling and effector cells such as the Paneth cell and the M cell.

Table 1. Soluble Immunoregulatory Products of the GALT

Cell Source	Mediator
Mucosal T cells	IL-2, 4, 5, Interferon gamma, IL-6, TNF
Mucosal mast cells	TNF, histamine
Macrophages	IL-1, Granulocyte-macrophage CSF
Paneth cells	TNF, Lysozyme, Defensins
Neural tissues	Neuropeptides- VIP, Somatostatin, Substance P
Dietary casein	Beta casomorphin

Intestinal lymphocytes comprise three separate compartments: the intraepithelial lymphocytes which are almost exclusively T cells, the majority of which are CD8 positive [90]; the lamina propria lymphocytes which include both T and B cells [91]; and the specialized aggregations of lymphocytes known as Peyer's patches. Lymphocytes of the GALT differ from those found in the peripheral circulation in a number of important respects. In rodents, T cells bearing the gamma/delta receptor predominate among the intraepithelial lymphocytes [92], although the same is not true in humas [93]. Intestinal T cells, unlike their circulating counterparts, are preferentially activated via the CD2 rather than the CD3 receptor [94]. They produce large amounts of IL-5 which regulates B cell differentiation to secrete IgA [95]. Production of this cytokine is usually associated with the Th2 subset of helper T cells, however CD8+ gamma/delta intraepithelial T cells also produce IL-5 both constitutively and in response to engagement of the CD3 or CD8 receptor [96]. A unique subset of T cells found in Peyer's patches, the contrasuppressor T cell, plays an important role in facilitating local immune responses in the face of immune interactions which induce systemic tolerance [97].

Intercellular signalling by the release of soluble mediators is critical to the coordination and expression of mucosal immunity [98]. Cells of the gut associated lymphoid tissues are a rich source of immunologically active mediator molecules (Table 1). In addition to IL-5, normal intestinal T cells release interferon gamma, TNF [99], IL-2 and -4 [94], and IL-6 [95]. These same cytokines may contribute to local disease. Increased numbers of cells secreting TNF are seen in patients with Crohn's disease [100] and local mucosal injury in graft versus host disease can be prevented by antibodies directed against interferon gamma [101]. Macrophages are found throughout the GI tract and are likely the source of increased amounts of IL-1 and GM-CSF produced by intestinal mononuclear cells from patients with inflammatory bowel disease [102].

Other cell populations in the gut mucosa play a role in local immunity. An important antibacterial role for Paneth cells is suggested by the fact that they express mRNA for TNF, and have been shown to contain both lysozyme and antibacterial defensins [103]. Mucosal mast cells also synthesize and release large quantities of TNF [104]. Moreover, neuropeptides such as substance P [90] and even exogenous compounds such as the milk-derived peptide beta-casomorphin [105] are able to exert a significant regulatory influence on immune responses within the intestinal mucosa.

The influence of the luminal flora on the production and release of cytokines by the GALT has not been studied, although emerging data regarding the rich immunoregulatory repertoire of these tissues suggest that interactions between the GALT and its environment are highly probable.

The Liver and the Mediator Response of MOF

The fetal liver is an important organ of extramedullary hematopoeisis. This function ceases by the time of birth, however the liver retains a critical role as an effector of antibacterial immunity, and a regulator of systemic immune homeostasis. It also figures prominently in the metabolic and immunologic alterations accompanying the septic response.

A variety of stimuli including infection, tissue injury, sterile inflammation, and pregnancy evoke a characteristic pattern of altered hepatocyte protein synthesis known as the acute phase response. Synthesis of acute phase reactants such as C reactive protein, alpha-1 antitrypsin, fibrinogen, ceruloplasmin, ferritin, and haptoglobin is increased, while the synthesis of albumin, LDL, and HDL is decreased. The acute phase response is highly

Table 2. Secretory Products of Kupffer Cells

Cytokines	IL-1 IL-6 IL-8 TNF Interferon Alpha/Beta Transforming Growth Factor Beta
Bioactive Lipids	Prostaglandin D2 Prostaglandin E2 Thromboxane A2 PAF
Cytokine Inhibitors	IL-1 inhibitor
Complement Components	
Reactive Oxygen Intermediates	
Reactive Nitrogen Intermediates	

conserved, being found in invertebrates as well as vertebrates [106], although its biological role is poorly understood. Certain of the acute phase reactants, notably C reactive protein [107] and alpha-1 antitrypsin [108] demonstrate immunmodulatory activity *in vitro*, while the negative acute phase reactant high density lipoprotein binds endotoxin and slows its removal by the reticuloendothelial system [109]. Whether these represent adaptive responses to invasive infection, maladaptive responses which impair host defense, or mere *in vitro* curiosities is unknown.

The acute phase response is initiated by IL-6, a major secretory product of endotoxin-activated Kupffer cells [110]. Activated Kupffer cells release a remarkable array of biologically active mediators including the proinflammatory cytokines IL-1, IL-6, and TNF, prostaglandins, thromboxane A2, platelet activating factor (PAF), and intermediates of oxygen and nitrogen (Table 2) [111, 112]. Kupffer cell products may act in an autocrine fashion to regulate subsequent Kupffer cell mediator release [113], in a paracrine fashion to alter hepatocyte protein synthesis [114] or release of factors such as nitric oxide [115], or in an endocrine fashion, affecting remote organs following their release into the systemic circulation [116].

The Kupffer cell mass comprises more than 70% of the total population of macrophages and monocytes in the human, and may, therefore, be the major site of synthesis of macrophage-derived mediators of MOF [112]. Indeed, studies in human volunteers show that systemic endotoxemia results in the release of TNF and IL-6 from the splanchnic circulation, splanchnic production accounting for as much as one half of total TNF release under these circumstances [117]. Hepatocyte products with immunoregulatory potential have also been described [118, 119], and liver injury is associated with a spectrum of immunologic abnormalities very similar to those occurring in MOF [120].

The liver plays an important role in antigen-specific tolerance. Portal administration of antigen results in suppression of both cell-mediated [121] and humoral [122] responses following subsequent immunization, and portal drainage of an allograft permits prolonged graft survival [123]. The mechanism is unknown, but may involve the release of an antigen-specific serum factor [124].

The Gut, The Liver, and Immune Dysfunction in MOF

MOF is associated with a complex spectrum of immunologic abnormalities and an enhanced susceptibility to invasive infection [112]. Impairment of cell-mediated immunity, manifested by a reduction in delayed type hypersensitivity (DTH) responsiveness *in vivo* [125] and of mitogen-stimulated lymphocyte proliferation *in vitro* [126], is a particularly prominent feature. We have investigated the potential contribution of gut-liver interactions to this systemic state of altered immune responsiveness.

Table 3. Differential Effects of Portal and Systemic Bacteremia on the Experimental Delayed Hypersensitivity Response. (Adapted from [128, 129] with permission)

	(DTH as % of Non-operated Controls)		
		Route of Infusion:	
Infusion	IVC	Portal	p.
Saline	59 ± 7	63 ± 6	NS
Live *E. coli*	59 ± 4	41 ± 9*	< 0.05
Killed *Ps.aeruginosa*	61 ± 4	48 ± 3*	< 0.05
Live *S. fecalis*	49 ± 5*	60 ± 4	< 0.05
Carrageenan	61 ± 4	79 ± 8*	< 0.05

Mean ± SEM

In rats which have been presensitized to the experimental antigen, keyhole limpet hemocyanin (KLH), the induction of peritonitis by cecal ligation without puncture produces significant suppression of DTH reactivity to KLH, and massive jejunal overgrowth with *E. coli*. By suppressing the animal's endogenous *E. coli* with oral antibiotics and then repopulating the gut with antibiotic-resistant *E. coli*, we were able to show that the small bowel overgrowth induced by cecal ligation contributed to the observed DTH suppression [32]. Similarly, prolonged feeding of killed *Pseudomonas* or *Candida*, but not *S. epidermidis* or sheep red blood cells, resulted in significant suppression of DTH responsiveness [127], independent of bacterial viability.

Suppression of *in vivo* and *in vitro* cell-mediated immunity could also be induced by infusion of gram-negative bacteria into the portal vein, but not into the systemic circulation. Rats received an infusion of organisms into either the systemic circulation via the infrahepatic vena cava, or the portal circulation via the portal vein (Table 3). When the challenge organism was live *E. coli* or killed *Pseudomonas aeruginosa*, delayed hypersensitivity responses were significantly depressed in portally-infused animals, whereas responses in systemically-infused animals did not differ from control values; suppression was not seen when the organism was a gram-positive bacterium, *S. fecalis*. *In vivo* ablation of Kupffer cell responsiveness by administration of carrageenan significantly reduced the magnitude of DTH suppression resulting from surgery [128, 129].

Suppression of mitogen-stimulated lymphocyte proliferation was also evident 24 h following portal but not systemic infusion of killed *Pseudomonas* (Fig. 1). Splenocytes isolated from portally-infused animals failed to proliferate when stimulated *in vitro* with the T cell mitogen, concanavalin A, and responses to the B cell mitogen LPS were reduced; splenocytes from systemically-infused animals responded normally to mitogenic stimulation. The suppressive influence present in the cultures of spleen cells from portally-infused animals could be removed by depletion of splenic adherent cells. Mo-

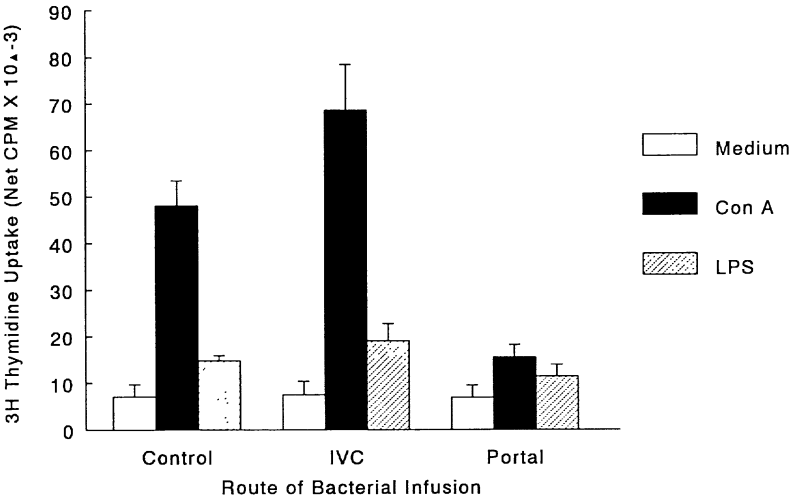

Fig. 1. Suppression of the proliferative response to the mitogens Con A and LPS of splenocytes isolated from rats 24 h following infusion of 3 x 10^8 killed *Pseudomonas aeruginosa* into either the infrahepatic vena cava or the portal vein. Responses in systemically (IVC) infused animals do not differ from those of their non-operated controls; portal infusion, however, induced marked suppression of *in vitro* proliferation.

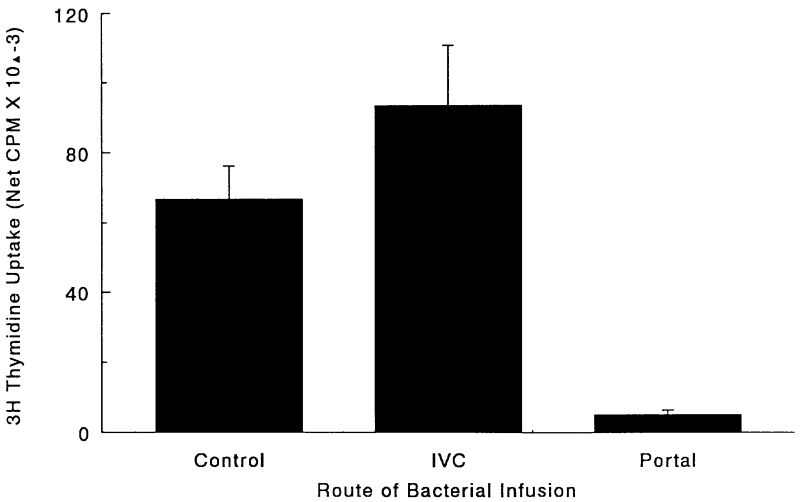

Fig. 2. Alveolar macrophages isolated from rats 24 h following infusion of *Pseudomonas aeruginosa* into the infrahepatic vena cava or portal vein. Macrophages from portally-infused animals release a potent soluble suppressor factor which can inhibit the mitogen-induced proliferative response of isolated splenocytes.

reover, alveolar macrophages harvested from portally-infused animals were shown to secrete significant amounts of a soluble factor which could almost completely inhibit proliferation of normal control splenocytes (Fig. 2) [130].

These studies demonstrate a potential role for the liver as a component of a biological cascade initiated by portal endotoxemia and resulting in the release of an immunosuppressive factor from remote macrophage populations. Endotoxin itself is not responsible for this suppressive influence, since LPS actually stimulates splenocyte proliferation in a dose-dependent fashion. Rather the process appears to involve the release of an hepatic factor which in turn promotes the release of a second factor or factors from remote macrophages. The identity of this second factor is under investigation: suppression can be overcome by a blocking antibody to transforming growth factor beta, but although TGFβ is necessary for suppression, it alone is not sufficient to induce suppression of the degree seen in the model.

Conclusion

The gut-liver paradigm provides a different perspective on the pathogenesis of the state of altered immune homeostasis which characterizes MOF. If classical invasive infection produces morbidity as a result of the interaction of invading organisms with host immune cells, an alternate pathway for this process may occur in the critically ill as a consequence of interactions between an altered gut flora and immune cells in the liver. The clinical importance of this gut-liver axis is, at present, impossible to quantitate in the absence of effective gut-directed interventions which might selectively inhibit it. Moreover, animal models of critical illness fail in many important respects to model the complex organ system interactions which characterize MOF as it evolves in the critically ill patient receiving intensive monitoring and therapy and maximal organ system support.

Clinical studies have largely focused on the role of the gut as a source of invasive infection in critical illness. A number of reports suggest that the risk of ICU-acquired infection can be minimized by measures taken to prevent gut bacterial overgrowth, although even this is controversial. Whether such measures can also attenuate the host response which produces organ dysfunction is unknown. Support of the gut mucosa by early enteral feeding has been shown to reduce rates of infectious complications, to reduce post-trauma bacteremia, febrile episodes, and pulmonary failure, and to attenuate the acute phase response following trauma. Yet it remains to be proven that enteral feeding can prevent MOF.

For the present, the most promising therapeutic advances seem to lie in the area of selective manipulation of the putative mediators of organ injury, independent of their anatomic site of production or of the pathological processes which triggered their release. Ultimately the importance of the gut-liver axis may lie not in the specific avenues it opens for novel means of therapy, but in the emphasis it focuses on the dynamic and constantly changing nature of the problems which lie at the frontiers of critical care.

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