Burns, Bacterial Translocation, Gut Barrier Function, and Failure

Louis J. Magnotti, MD, Edwin A. Deitch, MD

The development of systemic inflammation, acute lung injury, and multiple organ failure after a major thermal injury, as well as nonthermal forms of trauma, remain relatively common causes of morbidity and mortality. During the past two decades, increasing recognition that the ischemic gut may contribute to the development of sepsis and organ failure in burn patients, as well as other critically ill patient populations, has led to new hypotheses to explain burn-induced multiple organ failure as well as highlighted the importance of early enteral nutrition. Thus, the goal of this review will be to provide a perspective on the evolution of the gut hypothesis of systemic inflammation and distant organ dysfunction. (J Burn Care Rehabil 2005;26:383–391)

Our understanding of intestinal barrier function biology, its potential clinical importance, as well as the pathophysiology and consequences of gut barrier failure has changed considerably over the course of time. Now, it is clear that the intestinal mucosa functions physiologically as a local defense barrier to prevent bacteria and endotoxin, which normally are present within the intestinal lumen, from escaping and reaching extraintestinal tissues and organs. In addition, the loss of intestinal barrier function appears to play a role in the development of systemic infection and/or multiple organ failure (MOF) in selected patients.[1] More recently, it has become apparent that the ischemic and/or stressed gut can become a proinflammatory organ[2] and that gut-derived factors that are liberated after periods of splanchnic hypoperfusion can lead to acute distant organ and cellular dysfunction as well as to the activation of neutrophils and other proinflammatory cells.[3]

Although intestinally derived factors were proposed as important contributors to shock in critically ill and injured patients in the 1960s,[4] this notion generally was not accepted by the medical community and was largely ignored until the 1980s.[5] Renewed interest in gut barrier failure and bacterial translocation was based on clinical observations that trauma patients, burn patients, and critically ill patients, especially those developing the multiple-organ dysfunction syndrome (MODS), frequently had life-threatening bacteremias with enteric organisms in the absence of an identifiable focus of infection.[1] These clinical observations resulted in a large body of work investigating the relationships among gut barrier function, the intestinal bacterial flora, systemic host defenses, and injury in an attempt to delineate the mechanisms by which bacteria contained within the gastrointestinal (GI) tract can translocate to cause systemic infections.[6,7] From these and subsequent studies, the current role of the gut and gut barrier function in the prevention and potentiation of systemic infections and MODS have evolved.

THE GUT BARRIER AND BACTERIAL TRANSLOCATION

The gut is a complex organ, the primary function of which is the digestion and absorption of nutrients. However, in addition to nutrient absorption, the gut must function as a barrier to prevent the spread of intraluminal bacteria and endotoxin to systemic organs and tissues. Intestinal barrier function can be seen to be of major importance when one considers that the distal small bowel and colon contain enor-

From the Department of Surgery, University of Medicine and Dentistry of New Jersey–New Jersey Medical School, Newark, New Jersey
Address correspondence to Louis J. Magnotti, MD, Department of Surgery, University of Medicine and Dentistry of New Jersey–New Jersey Medical School, Newark, New Jersey 07103.
This work supported in part by NIH Grant GM 59841 (EAD) and DOD Navy Research Grant N00014-00-1-0878 (EAD).

0273-8481/2005

DOI: 10.1097/01.bcr.0000176878.79267.e8

mous concentrations of bacteria (10^{10} anaerobes and 10^5 to 10^8 each of Gram-positive and Gram-negative aerobic and facultative microorganisms per gram of tissue) and enough endotoxin to kill the host thousands of times over. Nevertheless, in a normal, healthy individual, gut-origin bacteremia and sepsis do not occur because the host has developed multiple defense mechanisms to prevent the bacteria that are colonizing the gut, as well as their products, from crossing the mucosal barrier and spreading to systemic tissues. Thus, under normal conditions, the intestinal mucosa functions as a major local defense barrier that helps prevent bacteria and/or endotoxin contained within the intestinal lumen from escaping and spreading to the extraluminal tissues and organs. However, under certain experimental and clinical circumstances, this intestinal barrier function becomes overwhelmed or impaired, resulting in the movement of bacteria and/or endotoxin to the mesenteric lymph nodes (MLNs) and systemic tissues. This process of bacteria and their products crossing the intestinal mucosal barrier and spreading systemically has been termed bacterial translocation.[8,9] The term "bacterial translocation" does not indicate a mechanism but instead is used to describe the phenomenon of bacteria crossing the mucosal barrier and is defined as the passage of viable indigenous bacteria from the GI tract to extraintestinal sites, such as the MLN complex, liver, spleen, and/or bloodstream.

Conceptually, the process of bacterial translocation occurs through a series of steps. In the initial step, luminal bacteria adhere to the epithelial cell surface or to ulcerated areas of intestinal mucosa. Once adherence to the epithelium has occurred, the bacteria must then cross the mucosal barrier and reach the lamina propria in a viable state. It is at this point that bacterial translocation has technically occurred. However, unless these bacteria can successfully spread from the lamina propria to systemic organs, the process is of no clinical significance. In response, the host has developed a complex series of defense mechanisms that function together to prevent potentially pathogenic bacteria from adhering to the intestinal mucosa. These defense mechanisms of the gut barrier provide four generalized levels of protection: these are the stabilizing influence of the normal intestinal bacterial flora, mechanical and immunologic defenses, and the gut–liver axis (Table 1).

The underlying mechanisms of how and under what circumstances bacteria contained within the gut translocate across the mucosal barrier have been studied extensively in a number of animal models, including models of thermal injury. In fact, although bacterial translocation can be induced in a variety of animal models, it appears that at least one of three basic pathophysiologic factors must be present for it to occur.[6] These basic conditions include:

1. Disruption of the normal gut flora, resulting in bacterial overgrowth with Gram-negative enteric bacteria,
2. Physical disruption or impairment of the gut mucosal barrier and/or
3. Impaired host immune defenses.

Of clinical importance, the same conditions documented to promote loss of gut barrier function and bacterial translocation in experimental models are commonly present in critically ill or injured patients (Table 2). These patients frequently are immune suppressed, and the antibiotic regimens they receive may disrupt the normal ecology of the gut microflora, resulting in impaired colonization resistance and subsequent bacterial overgrowth by potential pathogens. Current stress ulcer-prevention therapy may result in abnormal colonization of the stomach with bacteria and may permit the increased survival of orally ingested bacteria. Hyperosmolar enteral or parenteral feeding may not only disrupt the normal bacterial ecology of the gut but also may alter the mechanical defenses of the intestine. The use of vasoactive drugs may cause a decrease in splanchnic blood flow, resulting in ischemic injury to the gut epithelium and loss of the epithelial barrier. The hypoalbuminemia and capillary leak syndrome that commonly occur in critically ill patients could produce intestinal edema, resulting in impaired jejunoileal peristalsis, intestinal stasis, bacterial overgrowth, and altered gut permeability to intestinal luminal contents. In addition, hepatic failure or obstructive jaundice may allow endo-

Table 1. Components of the gut barrier

Microbial (normal gut flora)
Contact inhibition
Colonization resistance
Mechanical
Mucus layer
Peristalsis
Epithelial barrier
Junctional complexes
Desquamation
Immunologic
Gut-associated lymphoid tissue (GALT)
Secretory immunoglobulins
Gut-liver axis
Bile salts
Reticuloendothelial function

Table 2. Clinical conditions altering gut barrier function

Antibiotics
Disruption of normal gut microflora
Impaired colonization resistance
Bacterial overgrowth
Stress ulcer prevention
Disruption of normal gut microflora
Hypoalbuminemia/capillary leak
Intestinal edema
Impaired peristalsis with stasis
Bacterial overgrowth
Altered gut permeability
Hyperosmolar feeding
Disruption of normal gut microflora
Impaired peristalsis
Vasoactive drugs
Loss of mechanical epithelial barrier

toxin to reach the systemic circulation, where it may induce a septic-like state. Thus, these and other conditions commonly seen in critically ill patients may promote failure of the gut mucosal barrier to bacteria and endotoxin.

A second important concept that has evolved from these preclinical animal studies is that bacterial translocation is not an all-or-nothing phenomenon. The disruption or impairment of a single major intestinal defense system generally will promote bacterial translocation to the MLN and rarely to the liver or spleen. However, the translocating bacteria do not usually multiply in the MLN or spread systemically. Instead, they are locally contained and eventually eradicated as the host recovers. In conditions that more closely mimic the clinical situation, in which animals receive several simultaneous or sequential insults, translocating bacteria not only reach the MLN but also invade systemic organs. In some of these combined injury models, the animals survive, although bacteria can be transiently recovered from the liver and spleen. In other models, such as thermal injury[10] or protein-malnourished mice[11] receiving an otherwise-nonlethal dose of endotoxin, death frequently occurs from translocating bacteria.

Although both an intact epithelial barrier and a normal functioning immune system are important for adequate gut barrier function, it appears that an intact mucosa is of primary importance because an intact mucosal barrier will prevent bacterial translocation even in rats with selectively impaired cell-mediated immunity.[12] Thus, the physical barrier function of the mucosa appears to be of primary importance in preventing or limiting bacterial translocation, especially in a host with a normal gut flora, whereas the immune system appears to serve a secondary or supportive role to the intestinal mucosal barrier. This structure would not be surprising, because a similar role is played by other mechanical barriers, such as the skin.

One factor that most of the stress and injury models of bacterial translocation share is reduced splanchnic blood flow, leading to an ischemia–reperfusion-mediated gut injury with histologic evidence of mucosal edema and frequently villous tip destruction. The importance of this loss of mucosal barrier function in the pathogenesis of bacterial translocation after thermal injury,[13,14] hemorrhagic shock,[15] or endotoxin challenge[16] is underscored by the results of studies documenting that bacterial translocation can be largely prevented by limiting mucosal injury. In fact, in these models, mucosal injury appears secondary to a gut ischemia–reperfusion injury which is mediated, at least in part, by xanthine oxidase-generated oxidants.

Although modest levels of nitric oxide are beneficial in maintaining optimal microcirculatory blood flow, activation of the inducible form of nitric oxide (NO) synthase, leading to highly increased production of NO, has been implicated in the pathogenesis of gut injury, intestinal barrier dysfunction, and bacterial translocation.[17,18] Large amounts of NO may lead to intestinal mucosal injury in a variety of ways. For example, prolonged exposure of cells to large amounts of NO may cause cellular damage in a paracrine or autocrine fashion, inhibit cellular respiration, cause maldistribution of regional blood flow, increase gut permeability, and result in the increased production of the oxidant peroxynitrite.[19] The generation of peroxynitrite from NO requires the presence of increased levels of the oxygen-free radical superoxide, which is produced by intestinal xanthine oxidase in conditions associated with ischemia–reperfusion of the gut. Thus, altered mesenteric blood flow, resulting in an ischemia–reperfusion injury, mediated by xanthine oxidase-generated oxidants and the increased production of nitric oxide, appears to be a common pathway of mucosal injury, gut inflammation, and bacterial translocation. Consequently, a major concept that has evolved from these studies is that because the splanchnic circulation is sensitive to alterations in intravascular volume, injury- or stress-induced splanchnic vasoconstriction may ultimately lead to an ischemia–reperfusion injury of the intestinal mucosa and thereby result in impaired intestinal barrier function and intestinal inflammation.

RELATIONSHIP OF NUTRITION TO GUT BARRIER FUNCTION

Because of the potentially important relationship among nutrition, thermal injury, and gut barrier function, this area continuously has received increasing clinical and experimental attention during the past two decades. In fact, the recognition of the concept of gut barrier failure and bacterial translocation was one of the major impetuses that led to the initiation of early enteral feeding of burn patients shortly after injury.[20] Before this, it was thought that feeding should not be started during the first 48 to 72 hours after burn or after injury because of the belief that there was an obligatory pan-intestinal ileus. As stated earlier, gut barrier failure may result from one or more of the following three basic pathophysiologic conditions: 1) disruption of the normal ecologic balance of the indigenous gut microflora, with resultant overgrowth of Gram-negative enteric bacilli; 2) impaired host immune defenses; and 3) physical disruption of the gut mucosal barrier. Each of these variables may be affected by various dietary factors and/or the host's nutritional status. In fact, the optimal functional and structural integrity of the GI tract depends on whether or not the gut is fed enterally. Enteral feeding supports intestinal structural integrity by maintaining mucosal mass, stimulating epithelial cell proliferation, maintaining villus height, and promoting the production of brush border enzymes. Functional integrity of the mucosa also is supported by enteral feeding in several ways, including through the maintainence of tight junctional integrity between the intestinal epithelial cells, stimulation of blood flow to the gut, and the production and release of a variety of endogenous agents, such as cholecystokinin, gastrin, bombesin, and bile salts, all of which exert a major trophic effect on the intestinal epithelium.[21,22] In fact, experimental evidence exists stating that nutritional variables have a profound impact on gut barrier function. For example, starvation and protein malnutrition have been documented to impair host immune and antibacterial defenses, disrupt the normal ecology of the gut microflora, and lead to mucosal atrophy.[22] Consequently, one finding from the experimental studies on the relationship between nutrition and the gut is that enteral feeding preserves intestinal barrier function better than parenteral feeding. Additionally, animal studies have demonstrated that immediate enteral feeding after thermal injury reduces the hypermetabolic response by maintaining gut mucosal mass and preventing the excessive release of catabolic hormones.[23] Thus, because nutritional problems are relatively common in severely traumatized or critically ill patients, the resultant alteration in intestinal barrier function are likely to be of extreme clinical importance.

The role of selective intestinal malnutrition in the evolution of gut failure largely began with the work of Kudsk et al[24] in the late 1970s and early 1980s. They documented that animals fed enterally survived a septic challenge better than animals fed an identical diet parenterally. This experimental observation that parenteral feeding was associated with more infectious complications than enteral feeding has been verified in several prospective randomized clinical studies involving burn[25] and trauma patients.[26] The ability of high-protein enteral feedings to improve the clinical outcome in burn patients was first demonstrated conclusively in 1980 by Alexander et al[25] in a prospective study of burned children assigned randomly to receive either enteral or parenteral nutritional support. The enterally fed children had less impairment of their systemic immune defenses, fewer infectious complications, and increased survival. These studies and the results of other human and animal studies indicate that the route by which patients are fed may influence the immunoinflammatory and metabolic response to injury as well as the incidence of infectious complications and thereby modulate clinical outcome.

Because a significant component of the morbidity and mortality of severely burned patients may be connected to hypermetabolism and catabolism with its accompanying impairment of wound healing and increased infection risks, nutritional support and other strategies to prevent catabolism have become a major focus in the care of severely burned patients. Today there is overwhelming evidence that enteral nutrition is far superior to the parenteral route in burn patients. In fact, TPN has been shown to be ineffective in preventing the catabolic response after thermal injury and to instead enhance the stress response, increase endotoxin translocation, and impair mucosal immunity.[27] More notably, in burned patients, supplemental parenteral nutrition leads to a significant increase in mortality (63% vs 26%).[28] In contrast, the provision of enteral nutrients shortly after burn injury has been shown to reduce caloric deficits and may, in turn, stimulate insulin secretion and protein retention during the early phase after burn injury.[29] In addition, immediate high-calorie enteral feeding in the post-burn shock phase has a positive effect on splanchnic perfusion.[30] Clearly then, enteral nutrition by optimally feeding the gut as well as the rest of the body may be one of the best ways of protecting the immune-compromised, stressed, or thermally injured patients. Thus, on the basis of the clinical as well as the experimental literature, total enteral nutrition

starting as early as possible, without any supplemental parenteral nutrition, is the preferred feeding approach for burn patients.

PATHOPHYSIOLOGY OF BURN-INDUCED LOSS OF GUT BARRIER FUNCTION

Cutaneous burn injury causes gut mucosal atrophy, alters mucosal integrity, and leads to a breakdown in mucosal defense mechanisms. This breakdown has been blamed for the translocation of indigenous gut bacteria and the occurrence of septic complications and MOF in burn patients. The magnitude of bacterial translocation to MLN, liver, and spleen has been shown to be proportional to the severity of the burn injury.[13] Thermal injury also is associated with mesenteric vasoconstriction, and the postburn mesenteric vasoconstriction results in gut mucosal damage and an increase in bacterial translocation. In fact, after major burns, there is a transient and selective splanchnic vasoconstriction, which in turn is associated with intestinal mucosal acidosis, increased bacterial translocation, and endotoxin absorption from the gut.

Bacterial translocation has been demonstrated after thermal injury in many animal models, including rats,[21] sheep,[31] and pigs.[32] In the larger animal models, this phenomenon has been related to a decrease in mesenteric blood flow at the time of burn and subsequent insults. The relevance of these findings to the human experience remains controversial. However, studies in burn patients have shown that intestinal permeability is increased in patients with major thermal injuries shortly after the burn[33] as well as during episodes of infection.[34] Additionally, clinical studies have found a correlation between the extent of the burn injury and the degree of increased gut permeability,[35] as well as an association between the magnitude of the increase in gut permeability and the susceptibility to infection.[36]

Although bacterial translocation has been demonstrated consistently in experimental animal models, its occurrence in humans is uncertain and its precise role in the specific mechanisms involved in distant organ dysfunction is unclear. Although human studies measuring bacterial translocation to the MLN are limited, they do suggest that many of the conditions associated with bacterial translocation in experimental models do occur in patients. For example, translocating bacteria have been recovered from a relatively high percentage of patients with small bowel obstruction[37] or inflammatory bowel disease.[38] In these same studies, only 5% of elective surgery patients without bowel disease had viable bacteria recovered from their MLN, suggesting that bowel obstruction or inflammation is associated with bacterial translocation. In a recent study of 279 surgical patients, cultures of nasogastric aspirates were compared with those obtained from MLN taken at laparotomy as well as to the organisms recovered from subsequent infectious complications.[39] Bacterial translocation occurred in 21% of these patients and was significantly more frequent in those patients with multiple organisms in their nasogastric aspirates. Furthermore, in 45% of the postoperative septic complications, the same organism was identified in the MLN as the postoperative septic focus. Thus, proximal gut bacterial colonization appears to be associated with both increased bacterial translocation and septic morbidity. However, in trauma patients, the results of studies measuring bacterial translocation are less convincing. For example, in a large series of patients, with an injury severity score of 29, only 2% of 212 portal vein blood cultures were positive.[37] Seven of these positive blood cultures were presumed contaminants, and no endotoxin was identified in any of the portal vein blood samples, including blood samples from those patients who went on to develop organ failure. Thus, it was not possible to show an association between bacterial translocation and outcome, suggesting that bacterial translocation was not of clinical relevance in trauma patients.

There is, however, evidence that loss of gut barrier function is a real phenomenon in patients experiencing major thermal injury. In fact, the concentration of vasoconstrictive agents, such as catecholamines, glucagon, vasopressin, angiotensin, and thromboxane B_2 are elevated markedly immediately after burn injury and during subsequent insults. Also, as mentioned previously, studies in burn patients have found a correlation between the extent of the burn injury and the degree of increased gut permeability[35] as well as an association between the magnitude of the increase in gut permeability and the susceptibility to infection.[36] Furthermore, burn patients have an alarmingly high incidence of ischemic intestinal complications, as shown by an autopsy study of 161 burn patients.[40] In this study, 53% of the adults and 61% of the children were found to have ischemic intestinal pathologic findings at autopsy. In fact, these authors found that 16 patients had developed ischemic necrosis of their intestines necessitating laparotomy, with an associated 69% mortality.[40] Thus, the evidence indicating that gut barrier failure is a real phenomenon that contributes to morbidity and mortality after thermal injury seems real.

Nevertheless, the results of the clinical trial by Moore et al,[41] which failed to find bacteria or endo-

toxin in the portal blood of severely injured trauma patients, caused us and other to re-examine the concept of bacterial translocation, gut barrier function, and gut-origin sepsis. As will be described in the next section of this review, the studies performed to investigate why the portal blood of severely injured trauma patients was sterile and did not contain endotoxin led to a significant advance in our understanding of gut-origin sepsis and has generated the gut-lymph hypothesis of MODS.

THE GUT AS AN INFLAMMATORY ORGAN AND THE GUT-LYMPH HYPOTHESIS OF MODS

The gut origin hypothesis of MODS initially was based on the concept that gut barrier failure and intestinally derived bacteria and/or endotoxin translocating to the bloodstream and systemic tissues triggered a septic state and promoted the development of MODS (Figure 1A).[42] However, conflicting data from human studies indicated that translocating bacteria and endotoxin may not be primarily or exclusively responsible for the development of gut-induced MODS, even though there was compelling data from clinical trials of early enteral feeding, studies using gastric tonometry, and splanchnic-directed therapies that gut dysfunction was playing a major role in the pathogenesis of systemic sepsis and distant organ failure.[3] One possible explanation to resolve these disconcordant results is the possibility that gut-derived factors contributing to systemic inflammation and organ injury were reaching the systemic circulation via the mesenteric lymphatics rather than the portal venous system. This notion that nonbacterial gut-derived inflammatory factors are carried in the intestinal lymphatics rather than the portal circulation would explain the failure to detect endotoxin and/or bacteria in the portal blood of severely injured trauma patients, including those developing MODS,[40] while preserving the gut-sepsis hypothesis. This gut–lymph hypothesis is supported by previous experimental studies indicating that many gut-derived factors, including bacteria, exit the intestine via the intestinal lymphatics rather than the portal blood and that gut-origin bacteremia rarely was observed in animal models unless they were highly and rapidly lethal.

This concept that the mesenteric lymphatics and the proinflammatory properties of the gut were the missing links in the gut hypothesis of MODS has several conceptual consequences and led to a series of experimental studies directed at testing this concept. For example, one important conceptual consequence of the gut–lymph hypothesis is that the lung rather than the liver would be the first major vascular bed to be exposed to mesenteric lymph because mesenteric lymph reaches the systemic circulation via the thoracic duct, which empties into the subclavian vein and hence the pulmonary circulation. This concept that gut-derived toxic and inflammatory factors are reaching the systemic circulation via the intestinal lymphatics with the lung being the first organ exposed to these lymph factors was consistent with extensive clinical and experimental evidence documenting a strong link between gut ischemia/injury and the subsequent development of acute lung injury. In fact, during the last 6 years, we have conducted a large series of preclinical animal studies, including nonhuman primate studies,[43] showing that after hemor-

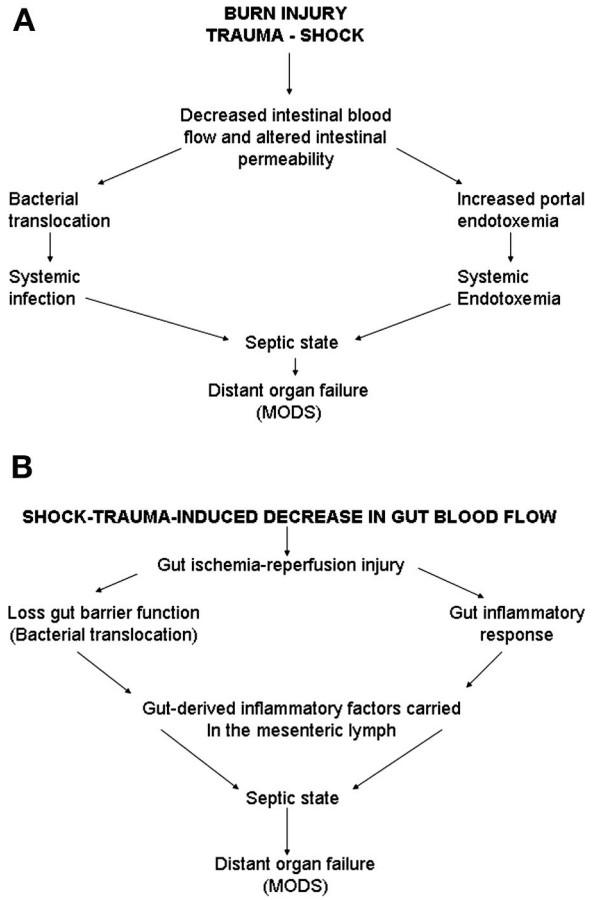

Figure 1. A. Schematic illustration of gut-origin hypothesis of sepsis and multiple organ dysfunction syndrome that is based on loss of gut barrier function and the systemic translocation of intestinal bacteria and endotoxin. B. Schematic illustration of the gut-lymph hypothesis of gut-origin sepsis and multiple organ dysfunction syndrome that is based on both loss of gut barrier function and the generation of proinflammatory factors by the ischemic gut, which reach the systemic circulation via the intestinal lymphatics.

rhagic shock, trauma, or a major burn injury, the gut releases proinflammatory and tissue injurious factors that lead to acute lung injury,[44,45] bone marrow failure,[46] myocardial dysfunction,[47] neutrophil activation,[48,49] red blood cell injury,[50] and endothelial cell activation and injury.[48,51] That is, factors released from the ischemic gut and carried in the mesenteric lymphatics, but not the portal vein, were able to recreate the findings observed in major trauma and burn patients and were sufficient to cause MODS. Thus, we found that many of the same insults that caused intestinal mucosal injury and promoted bacterial translocation were also able to induce the gut to produce biologically active, tissue injurious factors. Furthermore, we have found that the production of these biologically active, gut-derived factors occurs in the absence of recoverable bacteria or endotoxin in the portal or systemic circulations. Thus, the results of these studies have expanded the gut hypothesis beyond the original concept of bacterial translocation (Figure 1B).

The experimental approach used in these studies to test our gut-lymph hypothesis of MODS was 3-fold. First, we tested the ability of ligation of the main mesenteric lymph duct to prevent distant organ injury and systemic inflammation, because this maneuver would prevent gut-derived factors carried in the intestinal lymph to reach the systemic circulation. Second, we collected mesenteric lymph from rats and primates subjected to trauma–hemorrhage or burn injury and compared its ability to activate neutrophils, cause endothelial cell dysfunction, and inhibit bone marrow hematopoiesis and granulopoiesis to that of mesenteric lymph collected from animals subjected to sham-shock or sham-burn injury. Finally, by injecting mesenteric lymph from shocked rats into control animals, we tested the ability of biologically active lymph to recreate shock-induced organ injury and a systemic inflammatory response. The fact that mesenteric lymph duct ligation prevented burn as well as hemorrhagic shock-induced organ injury and cellular activation/dysfunction, whereas burn and shock lymph, but not sham-shock or sham-burn lymph, led to cellular injury in vitro provided strong support for the hypothesis that gut ischemia leads to the production of biologically active factors that are responsible for acute postshock and postburn organ dysfunction and systemic inflammation. Thus, these recent studies, coupled with the fact that gut injury leads to the gut becoming a proinflammatory factor-generating organ and that the intestinal vasculature can serve as a priming bed for circulating neutrophils, have led to a more complete understanding of the role of the gut in the pathogenesis of MODS.

At present, one major focus of our collaborative investigative energies is the isolation and characterization of the biologically active factors in mesenteric lymph as well as understanding the mechanisms by which these factors contained in lymph cause cellular injury. A second major direction has been the development of tissue-protective resuscitative strategies, with the goal of identifying and testing specific pharmacologic agents, which, when administered early after burn injury or hemorrhagic shock, would prevent or limit acute lung and other organ and cellular injury and/or dysfunction. To that end, we have found that certain types of resuscitative measures/therapies protect against distant organ injury after periods of intestinal ischemia–reperfusion. These therapies include the administration of hypertonic saline or albumin during the early resuscitation phase of therapy as well as the intraluminal inhibition of pancreatic proteases. That is, hypertonic saline resuscitation improved intestinal mucosa barrier function and ameliorated trauma–hemorrhage-induced gut and lung injury normally seen after conventional crystalloid resuscitation.[52] Similarly, low-dose albumin was shown to protect against shock-induced lung, endothelial cell, and red blood cell injury,[53] as was the intraintestinal administration of a pancreatic protease inhibitor.[54]

CONCLUSION

The gut barrier, when intact, functions to prevent the spread of intraluminal bacteria and endotoxin to systemic organs and tissues. The loss of gut barrier function has been implicated in the development of systemic sepsis and MOF. Maintenance of normal gut barrier function requires the complex interaction of numerous defense mechanisms, including the normal ecologic balance of the indigenous gut microflora, peristalsis, an intact mucus layer, an intact epithelial cell barrier, normal epithelial cell turnover, normal immune function, and the gut–liver axis. Numerous factors that complicate the care of the critically ill or injured patient may result in gut ischemia and/or impairment of gut barrier function. Therapeutic measures that aid in the support of gut barrier function include maintenance of an effective circulating blood volume, early definitive surgery, prompt recognition and control of infectious processes, the judicious and appropriate use of antibiotics, and optimal nutritional support.

Conceptually, the gut hypothesis of MODS has undergone multiple changes during the last several decades and has evolved from the concept of bacterial translocation being the dominant factor in gut-origin MODS to one in which gut ischemia and loss of bar-

rier function lead to the host producing endogenous proinflammatory and tissue injurious factors that lead to organ injury. In fact, gut ischemia appears to be the dominant link by which splanchnic hypoperfusion is transduced from a hemodynamic event into an immunoinflammatory event via the release of biologically active factors into the mesenteric lymphatics.

REFERENCES

1. Deitch EA. Multiple organ failure: pathophysiology and potential future therapies. Ann Surg 1992;216:117–34.
2. Deitch EA, Xu DZ, Franko L, et al. Evidence favoring the role of the gut as a cytokine generating organ in rats subjected to hemorrhagic shock. Shock 1994;1:141–6.
3. Deitch EA. Role of the gut lymphatic system in multiple organ failure. Current Opin Crit Care 2001;7:92–8.
4. Woodruff PW, O'Carroll DE, Koizumi S, et al. Role of the intestinal flora in major trauma. J Inf Dis 1973;128(S): S290–4.
5. Deitch EA, Berg RD. Bacterial translocation from the gut: a mechanism of infection. J Burn Care Rehab 1987;8:475–82.
6. Deitch EA. Bacterial translocation of the gut flora. J Trauma 1990;30:S184–9.
7. van Der Waaij D, Berghuis-de Vries JM, Lekkerkerk-van der Wees JEC. Colonization resistance of the digestive tract and the spread of bacteria to the lymphatic organs in mice. J Hyg Camb 1972;70:335–42.
8. Berg RD, Garlington AW. Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. Infect Immun 1979;23:403–11.
9. Deitch EA, Maejima K, Berg RD. Effect of oral antibiotics and bacterial overgrowth on the translocation of the GI-tract microflora in burned rats. J Trauma 1985;25:385–92.
10. Deitch EA, Berg RD. Endotoxin but not malnutrition promotes bacterial translocation of the gut flora in burned mice. J Trauma 1987;27:161–6.
11. Li M, Specian RD, Berg RD, Deitch EA. Effects of protein malnutrition and endotoxin on the intestinal mucosal barrier to the translocation of indigenous flora in mice. J Parenter Enteral Nutr 1989;13:572–8.
12. Maddaus MA, Wells CL, Platt JL, et al. Effect of T cell modulation on the translocation of bacteria from the gut and mesenteric lymph node. Ann Surg 1988;207:387–98.
13. Maejima K, Deitch EA, Berg RD. Bacterial translocation from the gastrointestinal tracts of rats receiving thermal injury. Infect Immun 1984;43:6–10.
14. Maejima K, Deitch EA, Berg RD. Promotion by burn stress of the translocation of bacteria from the gastrointestinal tracts of mice. Arch Surg 1984;119:166–72.
15. Baker JW, Deitch EA, Li M, Berg RD, Specian RD. Hemorrhagic shock induces bacterial translocation from the gut. J Trauma 1988;28:896–906.
16. Deitch EA, Taylor M, Grisham M, Ma L, Bridges W, Berg R. Endotoxin induces bacterial translocation and increases xanthine oxidase activity. J Trauma 1989;29:1679–83.
17. Sorrells DL, Friend C, Koltuksuz U, et al. Inhibition of nitric oxide with aminoguanidine reduces bacterial translocation after endotoxin challenge in vivo. Arch Surg 1996;131:1155–63.
18. Mishima S, Xu DZ, Lu Q, et al. Bacterial translocation is inhibited in inducible nitric oxide synthase knockout mice after endotoxin challenge but not in a model of bacterial overgrowth. Arch Surg 1997;132:1190–5.
19. Salzman AL. Nitric oxide in the gut. New Horiz 1995;3: 33–45.
20. McDonald WS, Sharp Jr., CW Deitch EA. Immediate enteral feeding in burn patients is safe and effective. Ann Surg 1991; 213:177–83.
21. Coffey Jr., JA, Milhoan RA, Abdula A, et al. Bombesin inhibits bacterial translocation from the gut in burned rats. Surg Forum 1988;39:109–10.
22. Deitch EA. Nutrition and the gut mucosal barrier. Curr Opin Gen Surg 1993;85–91.
23. Saito H, Trocki O, Alexander JW, et al. The effect of route of nutrient administration on the nutritional state, catabolic hormone secretion and gut mucosal integrity after burn injury. JPEN 1987;11:1–7.
24. Kudsk KA, Stone JM, Carpenter G, et al. Enteral and parenteral feeding influences mortality after hemoglobin *E coli* peritonitis. J Trauma 1983;23:605–9.
25. Alexander JW, MacMillan BG, Stinnett JD, et al. Beneficial effects of aggressive protein feeding in severely burned children. Ann Surg 1980;192:505–17.
26. Kudsk KA, Croce MA, Fabian TC, et al. Enteral versus parenteral feeding: effects on septic morbidity after blunt and penetrating abdominal trauma. Ann Surg 1992;215:503–13.
27. Sugiura T, Tashiro T, Yamamori H, Takagi K, Hayashi N, Itahashi T, et al. Effects of total parenteral nutrition on endotoxin translocation and extent of the stress response in burned rats. Nutrition 1999;15:570–575
28. Herndon DN, Barrow RE, Stein M, et al. Increased mortality with intravenous supplemental feeding in severely burned patients. J Burn Care Rehabil 1989;10:309–13.
29. Gottschlich MM, Jenkins ME, Mayes T, Khoury J, Kagan RJ, Warden GD. The 2002 Clinical Research Award. An evaluation of the safety of early vs delayed enteral support and effects on clinical, nutritional and endocrine outcomes after burns. J Burn Care Rehabil 2002;23:401–15.
30. Andel H, Rab M, Andel D, et al. Impact of early high caloric duodenal feeding on the oxygen balance of the splanchnic region after severe burn injury. Burns 2001;27:389–93.
31. Morris SE, Navaratnam N, Herndon DN. A comparison of effects of thermal injury and smoke inhalation on bacterial translocation. J Trauma 1990;30:639–45.
32. Tokyay R, Loick HM, Traber DL, et al. Effects of thromboxane synthetase inhibition on post-burn mesenteric vascular resistance in the rate of bacterial translocation in a chronic porcine model. Surg Gynecol Obstet 1992;174:125–32.
33. Deitch EA. Intestinal permeability is increased in burn patients shortly after injury. Surgery 1990;107:411–6.
34. Ziegler TR, Smith RJ, Mitchell CJ, et al. Increased intestinal permeability associated with infection in burn patients. Arch Surg 1988;123:1313–9.
35. Ryan CM, Yarmush ML, Burke JF, et al. Increased gut permeability early after burns correlates with the extent of burn injury. Crit Care Med 1992;20:1508–12.
36. LeVoyer T, Cioffi WG, Pratt L, et al. Alterations in intestinal permeability after severe thermal injury. Arch Surg 1992;127: 26–9.
37. Deitch EA. Simple intestinal obstruction causes bacterial translocation in man. Arch Surg 1989;124:699–701.
38. Ambrose NS, Johnson M, Burdon DW, et al. Incidence of pathogenic bacteria from mesenteric lymph nodes and ileal serosa during Crohn's disease surgery. Br J Surg 1984;71: 624–5.
39. MacFie J, O'Boyle C, Mitchell CJ, et al. Gut origin sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora and septic morbidity. Gut 1999;45:223–8.
40. Desai MH, Herndon DN, Rutan RL, Abston S, Linares HA. Ischemic intestinal complications in patients with burns. Surg Gynecol Obstet 1991;172:257–61.
41. Moore FA, Moore EE, Poggetti R, et al. Gut bacterial translocation via the portal vein: a clinical perspective with major torso trauma. J Trauma 1991;31:629–38.
42. Deitch EA. The role of intestinal barrier failure and bacterial translocation in the development of systemic infection and multiple organ failure. Arch Surg 1990;125:403–4.
43. Deitch EA, Forsythe R, Anjaria D, et al. The role of lymph

factors in lung injury, bone marrow suppression, and endothelial cell dysfunction in a primate model of trauma-hemorrhagic shock. Shock 2004;22:221–8.
44. Magnotti LJ, Upperman JS, Xu DZ, et al. Gut-derived mesenteric lymph but not portal blood increases endothelial cell permeability and promotes lung injury after hemorrhagic shock. Ann Surg 1998;228:518–27.
45. Magnotti LJ, Xu DZ, Lu Q, et al. Gut-derived mesenteric lymph: a link between burn and lung injury. Arch Surg 1999; 143:1333–41.
46. Anjaria DJ, Rameshwar P, Deitch EA, et al. Hematopoietic failure after hemorrhagic shock is mediated partially through mesenteric lymph. Crit Care Med 2001;29:1780–5.
47. Sambol JT, White J, Horton JW, Deitch EA. Burn-induced impairment of cardiac contractile function is due to gut-derived factors transported in mesenteric lymph. Shock 2002; 18:272–6.
48. Deitch EA, Shi HP, Lu Q, Feketeova E, Skurnick J, Xu da Z. Mesenteric lymph from burned rats induces endothelial cell injury and activates neutrophils. Crit Care Med 2004;32: 533–8.
49. Adams JM, Hauser CJ, Adams CA, Xu Dz, Livingston DH, Deitch EA. Entry of gut lymph into the circulation primes rat neutrophil respiratory burst in hemorrhagic shock. Crit Care Med 2001;29:2194–8.
50. Zaets SB, Berezina TL, Caruso J, Xu da Z, Deitch EA, Machiedo GW. Mesenteric lymph duct ligation prevents shock-induced RBC deformability and shape changes. J Surg Res 2003;109:51–6.
51. Xu DZ, Lu Q, Adams CA, Issekutz AC, Deitch EA. Trauma-hemorrhagic shock-induced up-regulation of endothelial cell adhesion molecules is blunted by mesenteric lymph duct ligation. Crit Care Med 2004;32:760–5.
52. Shi HP, Deitch EA, Da Xu Z, Lu Q, Hauser CJ. Hypertonic saline improves intestinal mucosa barrier function and lung injury after trauma-hemorrhagic shock. Shock 2002;17: 496–501.
53. Osband AJ, Deitch EA, Hauser CJ, et al. Albumin protects against gut-induced lung injury in vitro and in vivo. Ann Surg 2004;240:331–9.
54. Deitch EA, Shi HP, Feketeova E, Xu DZ. Serine proteases are involved in the pathogenesis of trauma-hemorrhagic shock-induced gut and lung injury. Shock 2003;19:452–6.