continued from page 3

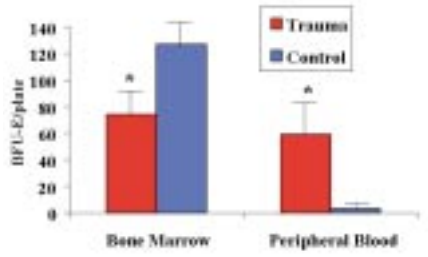

Figure 1: Erythroid burst forming cells (BFU-E) cultured from normal and trauma patients in the bone marrow and peripheral blood. Note the marked decrease in BM BFU-E and the loss of these progenitor cells into the peripheral blood.

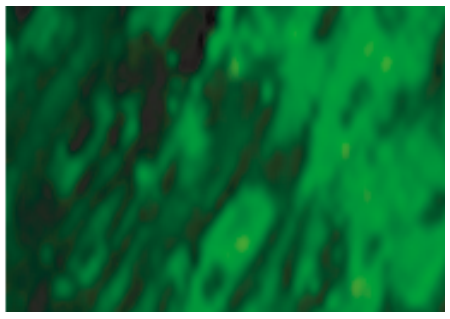

Figure 2: Representative immunofluorescence staining of the stromal culture demonstrates the predominance of fibroblasts.

experiments focused on these cells. Bone marrow stromal cultures from the trauma patients grew very poorly, if at all, compared to those from normal volunteers. The average time for the cultures to reach confluence was 10 days in the volunteers, compared to 21 days in the trauma patients. Up to 20% of trauma patients never reach confluence after 40 days in culture. In addition, the morphology of the stromal cultures from trauma patients was clearly different and showed a significant increase in fibroblasts (89±4% vs. 6±5%) and decrease in macrophages (5±2% vs. 20±2%) compared to controls. More importantly, these stromal cultures could not support the growth of early bone marrow cells, indicting that they were both phenotypically and functionally deficient. The loss of the stromal barrier may also explain the large number of hematopoietic progenitor cells that were recovered from the peripheral blood.

Most recently, we have identified the presence of bone marrow derived mesenchymal stem cells in peripheral blood of trauma patients, thus extending the loss of bone marrow cells to include not only hematopoietic cellular elements, but the supporting stromal architecture. Our future studies will focus on the mechanisms that account for the observed bone marrow failure and strategies to improve erythropoiesis following severe injury, so that after initial injuries are cared for, reliance on blood transfusions to maintain circulating red cell mass can become "a thing of the past."

David H. Livingston, MD, is the Wesley J. Howe professor and chief of the Division of Trauma in the Department of Surgery at UMDNJ-New Jersey Medical School (NJMS). He came to NJMS in 1988 after completing a fellowship in trauma surgery at the University of Louisville and a surgical residency at New York University Bellevue Hospital Medical Center. In addition to his research on bone marrow failure following injury, his work centers on trauma outcomes and prevention. Dr. Livingston has been awarded grants from the Agency for Health Care Policy Research as well as the National Institutes of Health. He is currently the chairman of the New Jersey Committee on Trauma of the American College of Surgeons and serves on the New Jersey EMS Council and the Governor's Medical Emergency and Disaster Prevention and Response Expert Panel. Dr. Livingston has been named in "Best Doctors of New Jersey" and has received the Public Service Award from the Brain Injury Association of New Jersey and a special commendation from the Federal Bureau of Investigation for the development of a model of medical support for FBI-SWAT activities.

FOR FURTHER INFORMATION, PLEASE VISIT OUR WEBSITE AT WWW.UMDNJ.EDU

EDWIN A. DEITCH, MD, PROFESSOR AND CHAIR, DEPARTMENT OF SURGERY, UMDNJ-NEW JERSEY MEDICAL SCHOOL AND CHIEF OF SURGERY, UMDNJ-UNIVERSITY HOSPITAL

Role of the gut in multiple organ dysfunction syndrome

by **Edwin A. Deitch**

As a student and surgical resident, I became fascinated with why otherwise healthy people died after a major injury or a disease such as pancreatitis. For this reason, upon completing my clinical training, I decided that I would focus the basic science component of my research career on sepsis and the host response to injury and infection. Over the ensuing 20 years, knowledge of the host response to injury, inflammation and infection evolved, resulting in the recognition that many of the same mediators that are induced during a life-threatening infection also occur after major trauma. A second critical insight during this time period was that the mediators leading to tissue damage, organ failure and death in these conditions are produced by the patient's own tissues and cells. Yet, the source of the initial factors leading to the sequence of progressive organ failure, as well as their identities, remained largely unresolved. My colleagues and I have identified the intestine as the major source of factors that trigger the acute septic response and organ failure in patients sustaining major trauma, burns or shock. This work has led to the gut hypothesis of multiple organ failure and has served as the focus of study by other investigative groups both here and abroad.

Multiple organ dysfunction syndrome or MODS

The past two decades have witnessed the emergence of a new syndrome termed multiple organ dysfunction syndrome, or MODS. This syndrome has reached epidemic proportions in most intensive care units

(ICUs) and is now the most common cause of death in the surgical ICU. Although MODS is responsible for 50-80% of all ICU deaths, our treatment options are mainly supportive, largely because of a failure to fully understand the pathophysiology of this syndrome. In fact, many practitioners, including myself, view MODS as a consequence of the success of modern medical care and our ability to prolong survival in patients with highly lethal injuries and diseases. As such, it represents a new clinical syndrome related to the prolonged survival of patients who would have previously died shortly after their injuries. In the 1980s I began studying the biology of this new disease for which no effective therapy was available. Yet development of effective therapy is based on a sound understanding of the biology of the disease process and the mechanisms leading to its development and progression.

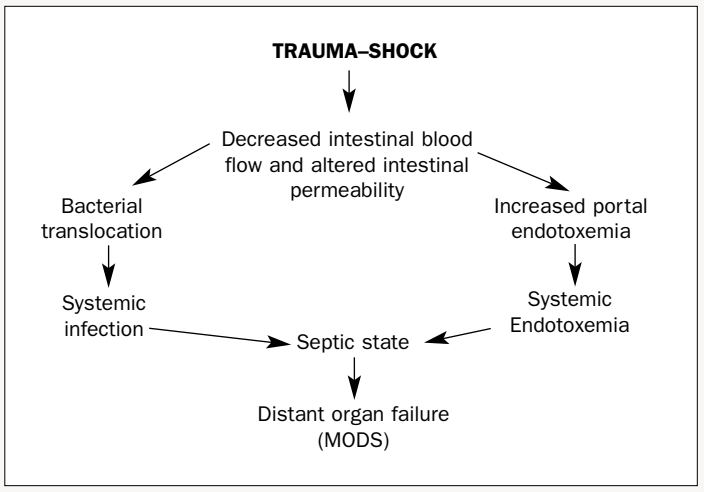

Figure 1: Schematic illustration of how loss of gut barrier function can lead to MODS via the systemic translocation of intestinal bacteria and endotoxin.

Gut-origin sepsis and the gut hypothesis of MODS

Working with a collaborator, Dr. Rodney Berg, I began studies in the early 1980s testing the idea that gut bacteria and their products could be an important trigger for the development of sepsis and MODS in critically injured or burned patients. The concept of gut-induced sepsis was that during shock or stress states, the body's response was to decrease blood flow to the intestines, thereby ensuring sufficient blood flow to critical organs such as the heart and brain. This decrease in intestinal blood flow, if sufficient in magnitude or depth, would lead to gut injury and loss of normal gut barrier function, causing the gut to become "leaky." This gut barrier failure in turn would allow bacteria and their toxic products, such as endotoxin, to escape from the gut and enter the systemic circulation, thereby causing systemic sepsis and leading to MODS. Considering that the normal gut contains enough bacteria and endotoxin to kill the host thousands of times over, we reasoned that even small increases in gut permeability could have profound physiologic consequences. Since the mechanisms by which intestinal bacteria crossed the intestinal mucosal barrier and spread systemically were unknown, we termed this process "bacterial translocation." Over the next 10 years, my laboratory and many others around the world began investigating this phenomenon and the term bacterial translocation became established in the literature. This concept of bacterial translocation was seized upon by many investigators, since it explained the clinical paradox of how MODS patients without a clinical focus of infection could have bacteria recovered from their blood or have a septic picture in the absence of microbial evidence of infection (Figure 1).

By the mid-1990s, I was one of a number of researchers who carried out patient studies showing that intestinal barrier function was lost in ICU patients after a major injury. Furthermore, several clinical studies showed a correlation between loss of gut barrier function and the development of systemic infection and MODS. Additionally, preclinical animal studies performed in my laboratory plus human clinical trials had established an important relationship between the route of nutrient administration, infection and gut barrier function. These studies established the importance of enteral feeding in high-risk patients, especially burn, trauma and ICU patients, and also the mechanisms by which lack of enteral feeding led to gut barrier dysfunction and bacterial translocation. It was during this period that many of the new commercial enteral formulas were developed and the risks of intravenous nutrition were recognized as well as the benefits of "feeding the gut" in addition to the rest of the body. Thus, within 10 years of my original studies, the concept of gut-origin septic states with

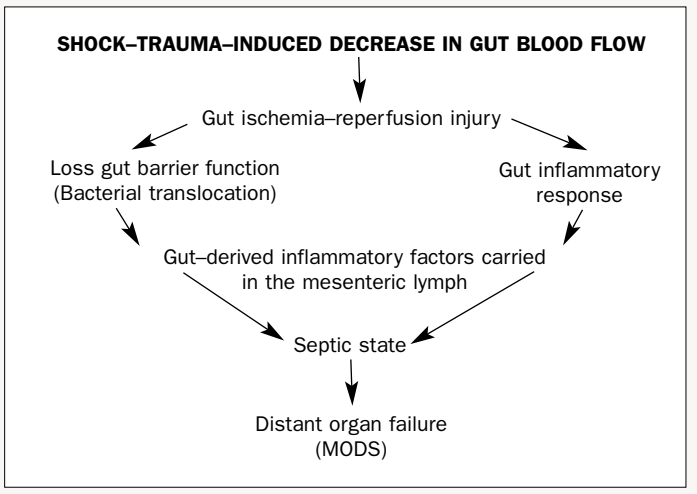

Figure 2: Schematic illustration showing the current model of the gut-lymph hypothesis of MODS.

the gut as the motor of MODS had emerged as one of the major conceptual advances in this field.

While the concept of bacterial translocation, with the systemic spread of gut-derived bacteria and their products, fit most of the data, it was not perfect. On the basis of the microbial concept of the gut hypothesis of MODS, it was logical to expect to find bacteria or endotoxin in the portal blood of patients with or at high risk of developing MODS. Yet neither was found in two clinical trials, causing me to begin to re-evaluate the concept of bacterial translocation. Based on the notion that the gut is the largest immune organ in the body, and our previous work indicating that many gut-derived factors, including bacteria, exit the intestine via the intestinal lymphatics rather than the portal blood, I proposed that the mesenteric lymphatics and the pro-inflammatory properties of the gut were the missing links in the gut hypothesis of MODS. Based on a large series of preclinical animal studies, including non-human primate studies, we were able to establish that after hemorrhagic shock, trauma, or a major burn injury, the gut released pro-inflammatory and tissue injurious factors that led to acute lung injury, bone marrow failure, myocardial dysfunction, neutrophil activation, RBC injury and endothelial cell activation and injury. That is, the factors released from the gut and carried in the mesenteric lymphatics, but not in the portal blood, were able to recreate the findings observed in major trauma or 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. In fact, we have found that conditions such as hemorrhagic shock and trauma cause production of these toxic gut-derived factors even in the

continued on page 6

continued from page 5

absence of recoverable bacteria or endotoxin in the portal or systemic circulations. Based on this most recent work, we have expanded the gut hypothesis beyond our original concept of bacterial translocation (Figure 2).

At present, one major focus of our collaborative investigative energies is the isolation and characterization of the biologically active factors in trauma-hemorrhagic shock 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 shock and trauma, would prevent or limit acute shock and trauma-induced lung and other organ injury. In both areas, our results are promising.

In summary, over the last 20 years, I have been involved with studies that have advanced the notion of gut-barrier failure from a theory in which bacteria translocate to reach distant organs to cause injury to one in which bacteria, gut ischemia or both invoke an intestinal response that contributes to MODS. In this paradigm, gut ischemia appears to be the dominant link by which a decrease in intestinal blood flow is converted from a localized hemodynamic response into a systemic inflammatory and immunologic event, and it does so via the release of unique, biologically-active factors into the mesenteric lymphatics.

Edwin A. Deitch, MD, is currently professor and chair of the Department of Surgery at UMDNJ-New Jersey Medical School. Prior to that, he was professor of surgery and director of trauma and burns at Louisiana State University in Shreveport. Dr. Deitch has been recognized as one of the "Best Doctors in the U.S.," "Best Doctors in New Jersey" and "Top Doctors in the New York Metro Area," since 1999. As a researcher, Dr. Deitch has been continuously funded by the NIH since 1983 and has published more than 280 peer-reviewed articles and three books. He has served as president of several national societies, including the Society of University Surgeons, The American Burn Association and the Shock Society. He is on the editorial board of nine professional journals and has been an invited speaker at more than 70 universities and medical schools in the U.S. as well as 33 international conferences.

FOR FURTHER INFORMATION, PLEASE VISIT OUR WEBSITE AT WWW.UMDNJ.EDU

STEPHEN F. LOWRY, MD, PROFESSOR AND CHAIR, AND STEVE E. CALVANO, PHD, ASSOCIATE PROFESSOR, DEPARTMENT OF SURGERY, UMDNJ-ROBERT WOOD JOHNSON MEDICAL SCHOOL

Parsing the injury response: from genes to phenotype

by **Stephen F. Lowry and Steve E. Calvano**

Injury is the most common cause of disability and death among children and younger adults. The economic costs of involuntary injury account for up to 10% of all heathcare expenditures and untold billions of dollars in terms of lost productivity. Despite these alarming statistics, research commitments devoted to injury prevention, care and rehabilitation significantly pale in comparison to the resources devoted to diseases of life-style and chronic illness. As our population ages, insights into the biology of injury across the entire age spectrum will undoubtedly become a national healthcare mandate.

We have been concerned with the problems of injury biology for more than 20 years. This interest arose initially from the study of burn victims whose unique physiology provides a paradigm of the adaptive response to injury. Burns and other significant injuries may result in manifestations of