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UMDNJ is unique. Its faculty forms a single healthcare university that staffs all three Level I trauma centers in New Jersey: UMDNJ-University Hospital in Newark, Robert Wood Johnson University Hospital in New Brunswick and Cooper Hospital/University Medical Center in Camden. Together, these three institutions account for more than half of all trauma center admissions in New Jersey. Taking advantage of the small geographic size of the state, the large number of patients and the rich academic affiliations has allowed the University to become a leader in innovative trauma research. Numerous investigators on all UMDNJ campuses benefit from this academically conducive environment, and are poised to bring new approaches and therapies to one of our most pressing public health issues.

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Anemia after injury: studies in erythropoietic suppression

by **David H. Livingston**

Successful erythropoiesis, or growth of new red blood cells, is a complex regulated process in which stem cells within the bone marrow proliferate and differentiate to mature red blood cells. The process requires the cooperation and interaction of hematopoietic stem cells, committed progenitors, differentiated immune cells, stromal cells and circulating factors in the plasma. One would expect the bone marrow of patients who lost blood to be "geared up" to manufacture fresh red blood cells. Therefore, it was a curious paradox that formerly healthy trauma patients were unable to generate sufficient red blood cells in response to severe trauma.

Blood loss and the subsequent need for blood replacement are common after serious injury, and trauma is one of the most common indications for transfusion. Blood loss is the defining feature of hemorrhagic shock. The need for ongoing transfusion following injury has clearly been shown to be a marker of subsequent organ failure and death. However, the administration of blood is not without its "price" as transfusions are immunosuppressive, costly and entail the risk of transmitting bloodborne infectious agents. Injury-associated anemia has long been thought to be due to the need for ongoing operative procedures, repeated phlebotomies, and the abbreviated age of banked blood. The acute use of blood following injury is necessary and life-saving and at the present time appears unavoidable. However, while less expected, the need for ongoing transfusion in the trauma patient is common and occurs long after acute injury and resuscitation. On any given day in the U.S., one of every seven intensive care unit (ICU) patients receives blood. In a study of trauma patients admitted to the Surgical Trauma ICU at UMDNJ-University Hospital, more than 80% received weekly blood transfusions.

For more than a decade, my laboratory has been interested in bone marrow failure following severe injury. Our original observations were that bone marrow erythropoiesis was seriously impaired for up to several days in rats subjected to trauma and hemorrhagic shock. The plasma obtained from these animals also appeared to inhibit the growth of bone marrow progenitor cells from normal rats. These early observations have been expanded to trauma patients admitted to the Surgical Trauma ICU at UMDNJ-University Hospital in an NIH-sponsored translational research study.

In one of our studies, we demonstrated that plasma obtained from critically injured patients is inhibitory to the growth of red and white blood cell progenitor cells. These findings replicate our work in experimental animals. The plasma appeared to exert part of its inhibitory effect on bone marrow stromal support cells (macrophages and fibroblasts). Furthermore, incubation of normal bone marrow stromal cultures with plasma from injured patients induced the negative hematopoietic regulator — TGF-β.

Bone marrow erythropoiesis following injury had never been systematically studied prior to the work in my laboratory. Over the past several years, we performed bone marrow aspirates on more than 80 patients between day 1 and 7 following severe injury. The bone marrow was cultured for early progenitor cells [cobblestone assay forming cells (CAFC) and long term cell initiating cultures (LT-CIC)], as well as for a later committed progenitor of erythroid [erythroid burst forming units (BFU-E) and erythroid colony forming units (CFU-E)], and myeloid (granulocyte-macrophage colony forming units CFU-GM) lineages. In all studies, progenitor cell growth was one third to one half of that in normal volunteers. In addition, we cultured the peripheral blood to ascertain if the bone marrow cells were leaving the bone marrow microenvironment. The greater number of cells in trauma patients than in normal volunteers indicates a loss of progenitor cells from the bone marrow.

Since the control of erythropoiesis is directed by the bone marrow stroma (supporting fibroblasts, endothelial cells, and macrophages), our next series of

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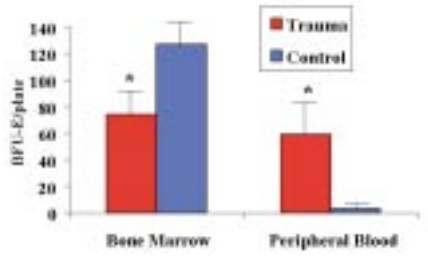

Figure 1: Erythroid burst forming cells (BFU-E) cultured from normal and trauma patients in the bone marrow and peripheral blood. Note the marked decrease in BM BFU-E and the loss of these progenitor cells into the peripheral blood.

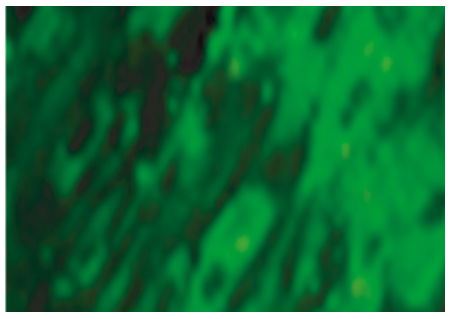

Figure 2: Representative immunofluorescence staining of the stromal culture demonstrates the predominance of fibroblasts.

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.

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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