Multiple Organ Failure

Pathophysiology and Potential Future Therapy

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Multiple organ failure (MOF) has reached epidemic proportions in most intensive care units and is fast becoming the most common cause of death in the surgical intensive care unit. Furthermore, in spite of the development of successive generations of new and more powerful antibiotics and increasing sophisticated techniques of organ support, our ability to salvage patients once MOF has become established has not appreciably improved over the last two decades. Clearly, new therapeutic strategies aimed at preventing or limiting the development of the physiologic abnormalities that induce organ failure are needed to improve survival in these critically ill patients. Based on our rapidly increasing knowledge of the mechanisms of MOF and the fruits of molecular biology, a number of new therapeutic approaches are in various stages of development. To effectively use these new therapeutic options as they become available, it is necessary to have a clear understanding of the pathophysiology of MOF. Thus, the goals of this review are to integrate the vast amount of new information on the basic biology of MOF and to focus special attention on the potential therapeutic consequences of these recent advances in our understanding of this complex and perplexing syndrome.

THE PAST TWO decades have witnessed the emergence of a new syndrome, termed multiple organ failure (MOF), which today represents the number 1 cause of death in surgical intensive care units. Although MOF is responsible for 50% to 80% of all surgical intensive care unit deaths and costs exceed $150,000 per patient, our treatment options are mainly supportive, and the basic pathophysiology of this syndrome remains to be fully elucidated.[1-3] In fact, the mortality rates of patients with established MOF or its close relative, the adult respiratory distress syndrome (ARDS), have not appreciably improved since their initial descriptions approximately 20 years ago.[4,5] Thus, at a time when spectacular advances in the field of organ transplantation have revolutionized the therapy of patients with end-stage single organ failure, our inability to successfully treat patients with acutely failed organs remains the major unsolved problem in the critically ill postoperative or postinjury patient.

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In many ways it is not surprising that, as our ability to support organ function and prolong survival in patients with highly lethal conditions has improved, we have uncovered new and unexpected clinical problems, such as MOF, for which no definitive therapeutic answers are initially available. Historically, one characteristic of surgical progress has been the identification, investigation, and subsequent conquest of new clinical problems. For example, in World War I the causal relationship between acute blood loss and irreversible "wound shock" was not known, and consequently acute shock was a common cause of death. Based on studies performed in the post-World War I period establishing the role of acute blood loss in the development of shock,[6] blood was used liberally during World War II to prevent and treat shock, thereby largely eliminating the previously common syndrome of irreversible wound shock. In spite of improved early survival, many of these patients went on to die of acute renal failure. During the Korean War, acute renal failure remained the most common cause of delayed death in successfully resuscitated patients and therefore was a focus of intense investigative activity. Basic experimental investigations on the pathophysiology of post-traumatic renal insufficiency[7] eventually led to the realization that injury-induced renal failure could be largely prevented by resuscitating these patients with sufficiently large amounts of crystalloids (to maintain an effective circulating intravascular volume and thereby maintain renal perfusion) in addition to blood. Thus, based on this better understanding of the physiology of injury and the need for acute volume resuscitation, acute renal failure was largely prevented in the Vietnam conflict. As more severely injured patients survived for longer periods, however, a new syndrome, post-traumatic pulmonary insufficiency (ARDS), emerged, and in the 1970s, the lungs became the organ system limiting survival.[5] Today, although the mortality

rate of patients with ARDS remains high, improvements in the management of these patients have resulted in the cause of death shifting from impaired gas exchange to MOF, and currently more than 75% of the patients dying with ARDS now die of MOF and systemic hemodynamic instability rather than of hypoxia.[8] Viewed in this light, MOF clearly represents the next, but surely not the last, obstacle that must be passed to improve survival in the critically ill surgical patient.

Although there is no substitute for good surgical technique and mature clinical judgment in optimizing survival, until we understand the basic pathophysiology of MOF, our ability to devise rational and effective therapeutic options will be severely constrained. Because MOF is at its most basic level a cellular disease mediated by protein and lipid molecules, our attempts to understand and eventually treat this bewildering and highly complex syndrome must include not just organ-based therapy but also must extend to the cellular and molecular levels. In large part, because of the scientific revolution brought on by molecular biology and the increasing availability of genetically engineered molecules, we already have made many important conceptual advances in our understanding of the basic biology of injury, inflammation, and immunology, which have shed light on the pathophysiology of MOF. For example, it is now clear that in MOF, organ injury is not directly due to exogenous factors, such as bacteria or toxins, but instead is largely a consequence of the host's own endogenously produced mediators. Thus, we are now in the exciting position of trying to integrate and extend these basic science advances into everyday clinical practice. In my opinion, the 1990s will see the transition of molecular biology from the laboratory to the clinic, and it is almost certain that molecular biologic therapies will become part of the therapeutic armamentarium of most practicing surgeons. It is with these thoughts in mind that I review some of the recent advances in our understanding of the biology and pathophysiology of MOF as well as the potential therapeutic options that have evolved or are likely to evolve from this basic research.

The Clinical Syndrome

Initial recognition of the MOF syndrome began with a report by Tilney et al. in 1973[4] describing the postoperative course of a group of patients with ruptured aortic aneurysms. In this publication, the observation was made that massive acute blood loss and shock could lead to the postoperative failure of initially uninvolved organs. This concept that a severe physiologic insult could result in damage to distant organs was formalized in a classic editorial by Baue[9] entitled "Multiple, Progressive, or Sequential Systems Organ Failure: A Syndrome of the 1970's." Shortly afterwards, Eiseman et al.[10] and Fry et al.[11] coined the terms "multiple organ failure" and "multiple system organ failure," respectively to describe this syndrome. Although initially proposed as a sign of occult or uncontrolled infection,[11,12] MOF has now been documented to occur after a number of diverse clinical conditions, including mechanical[13] and thermal[14,15] trauma, pancreatitis,[16] and shock.[17] Thus, although infection and shock are the two most common clinical predisposing factors, processes such as severe tissue injury or pancreatitis that induce a major inflammatory response appear capable of initiating a cascade of events that culminates in MOF.

Regardless of the cause, the syndrome of MOF generally follows a predictable course, beginning with the lungs and followed by hepatic, intestinal, and renal failure, in that order. Hematologic and myocardial failure are usually later manifestations of MOF, whereas the onset of central nervous system alterations can occur either early or late. Physiologically, these patients are hypermetabolic and they have a hyperdynamic circulation, which is characterized by an increased cardiac output and a decreased systemic vascular resistance. This classical sequential pattern of organ failure may be modified, however, by the presence of pre-existent disease or by the nature of the precipitating clinical event. For example, renal failure may precede hepatic or even pulmonary failure in patients with intrinsic renal disease or in patients who have sustained prolonged periods of shock, whereas hepatic or myocardial failure may be an early or even the initial manifestation of this syndrome in the patient with cirrhosis or myocardial damage. These clinical exceptions illustrate the important biologic principle that, although the systemic responses are similar among patients developing MOF, the exact sequence of organ failure can be influenced by the patient's acute disease processes or physiologic reserve. In addition, the temporal pattern of organ failure can be helpful clinically. For example, intra-abdominal infection is much more likely when clinical sepsis precedes the onset of pulmonary failure than when clinical sepsis develops after pulmonary failure.[8,11]

The criteria of organ failure or dysfunction vary from series to series, and this variability in the criteria used to define organ failure or even which organs should be used to evaluate prognosis adds confusion to an already complex field. Nonetheless, in almost all series, prognosis is related more to the number of organs that have failed than to any other variable, including the underlying process that initiated the MOF syndrome. For example, in Fry's original clinical report,[11] as the number of organs that failed increased from one to four, the mortality rate progressively increased from 30% to 100%. This concept has been verified and expanded in a prospective multiinstitutional study on acute organ failure involving 5677

medical and surgical intensive care unit patients.[18] In this study, not only was a direct relationship documented between the number of organs that failed and mortality rate, but the length of time the patient was in organ failure also correlated directly with mortality rate.

Although prognosis appears to be related directly to both the number of organs that fail and the length of time the patients are in organ failure, our ability to predict outcome in individual patients is not sufficiently accurate to supersede clinical judgment in determining when further treatment will be futile.[19,20] Furthermore, until we are able to accurately identify which patients will develop MOF before the onset of organ failure as well as be able to accurately predict outcome in individual patients with MOF, it will remain difficult not only to identify patients for whom further therapy is not warranted, but also to accurately evaluate the potential efficacy of new prophylactic or therapeutic treatment options. Because of the confusion and lack of consensus on what constitutes organ failure, I believe the time is appropriate to hold a consensus conference to define organ failure as well as to redefine certain terms, such as sepsis, whose meanings have become increasingly ambiguous as our understanding of the biology of the response to injury and stress has evolved. Nonetheless, Table 1 is one attempt to broadly define organ failure in which the degree of organ failure has been stratified into organ dysfunction (early) and advanced failure (late) stages.[11,13,17,18,21-24]

Cause, Biology, and Pathophysiology of MOF

General Concepts and the Role of Infection in MOF

Currently, one of the major factors limiting our ability to successfully treat patients with MOF is an incomplete knowledge of the biology and pathophysiology of this syndrome. Organ failure in this syndrome is unique in several respects: First, the organs that fail are not necessarily directly injured or involved in the primary disease process, and second, there is a lag phase of days to weeks between the initial or subsequent inciting events and the development of distant organ failure. These two clinical observations strongly indicate that MOF is a systemic process mediated by endogenous or exogenous circulating factors, the effects of which are not immediately apparent after the initiating physiologic insult. Because these patients appear to be clinically septic, and several groups have documented an association between an untreated septic focus and the development of MOF, it was proposed in the late 1970s that MOF was the external expression of an occult septic focus.[9,11,12] Although it is clear that an untreated or inadequately treated focus of infection can and commonly does cause MOF, it has become equally clear that not all septic-appearing patients who develop or die with MOF have untreated infections.[25] This is true of bacteremic as well as nonbacteremic patients. The critical role of infection as a mandatory initiator of this syndrome has been called into further question by clinical studies documenting that the identification and treatment of occult septic foci in patients with established MOF have not consistently improved survival.[21,26,27] Although uncontrolled infection is the initiating cause of MOF in about half of the patients, in the other half, MOF occurs either in the absence of a clinically identifiable focus of infection or the development of infection is a preterminal event of no apparent prognostic importance. These clinical paradoxes are summarized in Table 2.

Although the systemic clinical manifestations of MOF (fever, leukocytosis, hypermetabolism, and a hyperdynamic circulatory state) are all typical of gram-negative sepsis, a similar host response can be induced by other microorganisms, including gram-positive bacteria, viruses, and fungi as well as by stimuli that lead to an excessive and prolonged inflammatory response. Common noninfectious causes of MOF include pancreatitis, major thermal injuries, and polytrauma. For example, although most cases of pancreatitis are self-limited, a subgroup of these patients, in the absence of an identifiable focus of infection, develop a highly lethal fulminant systemic illness often associated with the development of MOF.[16] Similar observations have been made in trauma victims

TABLE 1. *Criteria of Dysfunction/Failure*

Organ or System	Dysfunction	Advanced Failure
Pulmonary	Hypoxia requiring respirator-assisted ventilation for at least 3–5 days	Progressive ARDS requiring PEEP >10 cm H_2O and FIO_2 >0.50
Hepatic	Serum bilirubin ≥2–3 mg/dL or liver function tests ≥ twice normal	Clinical jaundice with bilirubin ≥8–10mg/dL
Renal	Oliguria ≤479 mL/24 hr or rising creatinine (≥2–3 mg/dL)	Renal dialysis
Intestinal	Ileus with intolerance to enteral feeding >5 days	Stress ulcers requiring transfusion, acalculus cholecystitis
Hematologic	PT and PTT ↑ >25% or platelets <50–80,000	Disseminated intravascular coagulation
CNS	Confusion, mild disorientation	Progressive coma
Cardiovascular	Decreased ejection fraction or capillary leak syndrome	Hypodynamic response refractory to inotropic support

Based on references 11, 13, 17, 18, 21, 22, 23, and 24.

TABLE 2. *Clinical Paradoxes in MOF*

1. Organs that fail frequently are not directly injured in the initial insult.
2. There is a lag period of days to weeks between the initial insult and the development of organ failure.
3. Not all patients with clinical sepsis with MOF have microbiologic evidence of infection (septic state).
4. No septic focus can be identified clinically or at autopsy in more than 30% of bacteremic patients dying of clinical sepsis and MOF.
5. Identification and treatment of suppurative infections in patients with MOF may not improve survival.

by Goris et al.,[25] who documented that a focus of untreated infection was present in only about one third of trauma patients dying with MOF. These and other clinical and experimental observations have led to a reappraisal of the relationship of the septic response to infection. As a result, it is now generally accepted that (1) not all septic-appearing patients have an underlying infection, (2) large amounts of dead or injured tissue can replace bacteria as the stimulus for the septic response, and (3) it is frequently impossible to clinically differentiate the patient with systemic infection from the patient who appears septic, but does not have evidence of systemic infection.

Thus, one point deserving special emphasis is the remarkable physiologic similarities between systemic infection (classical sepsis), MOF, and a septic state in which there is no evidence of infection. Because all three conditions appear to share certain physiologic similarities, such as altered intermediary metabolism, a hyperdynamic circulation, and systemic signs of inflammation, it is likely that the mediators responsible for the external expression of these three clinical syndromes are similar. This assumption is strengthened by the observations that a classic septic response can be induced in normal human volunteers by the injection of inflammatory agents,[28] endotoxin,[29,30] or cytokines such as tumor necrosis factor (TNF).[31,32] Thus, one major recent conceptual advance is the recognition that sepsis and infection are not synonymous and that the septic state can occur in the absence of infection. For these reasons, investigators and clinicians have been begun using the terms "septic syndrome," septic state," or "mediator disease" to describe this phenomenon.[25,33,34] In fact, dissatisfaction with the ambiguous nature of the term "sepsis" has engendered a number of position papers as well as editorials, the goal of which is to redefine and clarify the terms used to describe the septic-appearing patient.[34–37] Although consensus has not been reached on the definition of sepsis, it is clear that sepsis does not equal infection and that infection is present in fewer than 50% of clinically septic patients.[36]

A second major conceptual advance is the realization that the host is not an innocent bystander or victim whose tissues are being directly ravaged by invading bacteria or products of injured tissue, but instead is an active participant in this destructive process. For example, until relatively recently, we believed that bacterial pathogens or their products, such as endotoxin, were directly responsible for the pathophysiologic manifestations of the septic response. It is now clear that cytokines and other mediators produced by the host in response to invading bacteria or their products are the direct mediators of the septic response, organ dysfunction, and MOF. This shift in thought has remarkable therapeutic implications. For example, using the paradigm that the host is an innocent bystander who is being directly injured by invading bacteria, the goal of immunomodulation would be to increase the host's inflammatory and immune responses and thereby bolster his or her ability to fight infection. In contrast, if the paradigm is modified to take into account that the host is being injured by an excessive or uncontrolled inflammatory response to invading bacteria, than the goal of immunomodulation will include attempts to modulate the host's immunoinflammatory response and thereby limit tissue injury. As will be discussed in more detail later, the realization that the host is destroying itself rather than being destroyed by bacteria has led to a research shift from attempts to understand and bolster a failing immune system to attempts to understand and selectively limit the host's uncontrolled or excessive inflammatory response.

A review of the potential relationships between infection and MOF would not be complete without a discussion of the role of empiric laparotomy in the patient with MOF. The concept, initially proposed by Polk and Shields in 1977,[12] that MOF is a valid sign of occult intra-abdominal infection led to a general belief that the presence of MOF in the absence of an identifiable focus of infection was an indication for an empiric laparotomy. As more patients with MOF without clinical or radiographic evidence of intra-abdominal sepsis were empirically explored, however, it became obvious that a large number of these patients did not have intra-abdominal infectious processes.[26,27] Thus, with the development of more sophisticated and reliable noninvasive imaging techniques, MOF does not mandate laparotomy when there is no clinical or radiographic evidence suggesting intra-abdominal disease. This is especially true when an alternative focus of infection has been identified, such as pneumonia. Nonetheless, there are certain patient groups in which intra-abdominal infectious processes are especially likely to be the cause of MOF. These include patients who have undergone elective or emergency abdominal surgery, especially when "sepsis" precedes pulmonary failure or the MOF syndrome evolves very rapidly.[8,10,11] In contrast, when ARDS is the first manifestation of MOF and precedes the septic response, occult intra-abdominal infection is less common. The decision of whether to operate is most difficult in the patient with a gram-negative enteric

bacteremia without an identifiable focus of infection. Although bacteremia in this circumstance clearly points to the gut microflora as the source of invading bacteria, it has become clear that in some circumstances bacteremia actually may be an expression of failed host defenses rather than of infection in the traditional sense. The realization that loss of intestinal barrier function and the subsequent escape (translocation) of bacteria from the gut to the systemic circulation can occur[38] has helped to explain the apparent paradox of why no septic focus can be identified clinically or at autopsy in more than 30% of bacteremic patients, including those dying with clinical sepsis and MOF.[25,39]

Mediators and Mechanisms of MOF

When evaluating the role of putative mediators and the accuracy of proposed mechanisms of MOF, it is important to keep two clinical observations in mind. First, infection is only one of several pathologic conditions that can initiate the cascade of events that culminate in MOF: Other conditions include endotoxemia, trauma with retained necrotic or injured tissue, and shock. Secondly, the septic response is not diagnostic of infection and can be induced by severe perfusion deficits as well as by the continued presence of dead and injured tissue. Based on these clinical observations and the host's limited repertoire of effector molecules, it is to be expected that the same or similar mediator systems are involved in the pathogenesis of organ injury even when the initiating events are different. Additionally, in attempting to understand the physiology of MOF, it is important to realize that the septic (hypermetabolic) response, ARDS, and MOF are not unrelated distinct entities, but instead appear to represent a physiologic continuum of progressively increasing severity.

Over the past two decades, multiple hypotheses have been proposed to explain specific aspects of the development of MOF. At first glance, many of these hypotheses seemed contradictory, yet as new information was generated and these hypotheses have been revised and refined, it has become possible to construct an integrated picture of the pathophysiologic processes involved in the evolution of organ injury. The basic elements of this proposed integrated scheme are an uncontrolled or persistent immunoinflammatory response and tissue hypoxia. A simplified version of this complex process is illustrated in Figure 1. First, there is an initiating clinical event that effects multiple normal homeostatic mechanisms. These altered, normally well-controlled, homeostatic systems interact to amplify or modulate each other. For example, during shock or periods of tissue hypoperfusion, oxygen delivery to the gut is impaired, resulting in intestinal injury[40] and increased intestinal permeability.[41] Increased permeability of the gut subsequently results in luminal bacteria and endotoxin reaching the portal and systemic circulations,[41,42] where they activate resident macrophages[43,44] and circulating neutrophils,[45,46] as well as activate multiple humoral plasma protein cascades.[47] Products of these activated leukocytes and protein cascades may in turn further impair oxygen delivery by their effects on the microcirculation,[48–50] as well as potentiate the continued translocation of bacteria or their products from the gut by increasing the degree of intestinal permeability.[51,52] A similar scenario may occur during infectious or inflammatory states, where activation of endogenous inflammatory mediators leads to changes in tissue oxygen delivery[50,53] as well as impairment of intestinal barrier function.[54] Therefore, it appears that under the right conditions, the cumulative disruption of multiple interacting systems may ultimately result in distant organ injury. A necessary corollary of this multifactorial hypothesis of MOF is that the prevention and treatment of

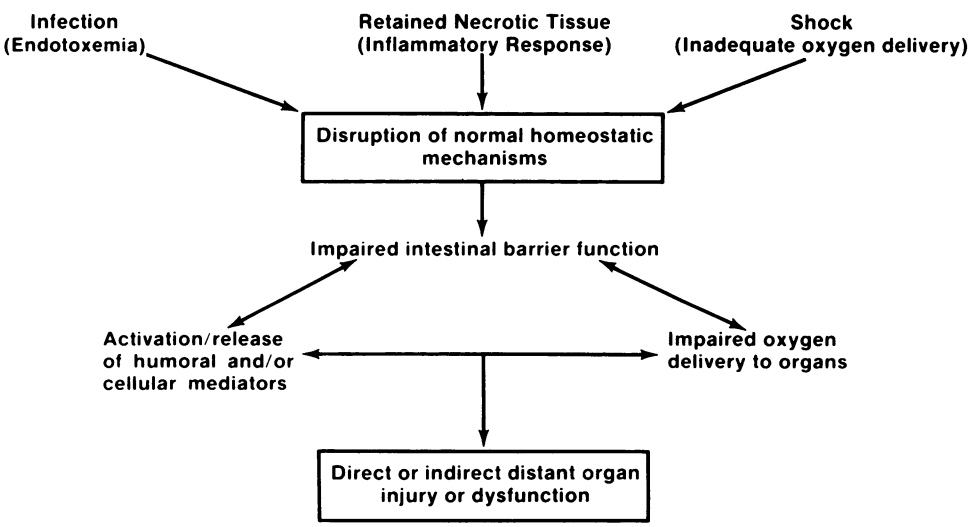

FIG. 1. Integrated paradigm of multiple organ failure.

MOF must be multimodal as well as directed at the cellular processes involved in organ injury.

Macrophage Hypothesis of MOF

In the macrophage hypothesis, excessive or prolonged activation or stimulation of macrophages ultimately results in excessive production, surface expression, and liberation of cytokines and other products, which through a cascade effect, involving additional humoral and cellular effector systems, exert deleterious local and systemic effects.[33,55] Although overproduction of cytokines and macrophage activation can have profound detrimental effects, cytokines also have beneficial effects. For example, both cytokines and macrophages are essential for normal antimicrobial and immune activity, wound healing, and optimal substrate mobilization (Table 3).[56]

The clinical correlate of the macrophage hypothesis of MOF is the uncontrolled inflammatory response. Normally, inflammation operates within a restricted environment to contain and eradicate infecting organisms and to clear damaged tissues of cell debris or foreign materials. Although generally beneficial to the host, inflammatory processes are intrinsically destructive to the surrounding tissues and thus can potentially result in major tissue injury. Furthermore, the inflammatory response can escape the local environment and induce a generalized systemic response, resulting in the activation of multiple inflammatory effector cells, including fixed tissue macrophages, neutrophils, and lymphocytes, as well as the activation of humoral protein cascades, most notably the coagulation and complement systems. Through this uncontrolled intravascular response, the vascular endothelium may be damaged, thereby further potentiating distant organ injury. Ultimately, systemic inflammation may become self-perpetuating because of both the continued "leak" or "spill-over" of locally or systemically produced inflammatory mediators into the circulation and inadequate regulation of the inflammatory response by the host. Although beneficial to the host, when proinflammatory mediators, such as TNF, interleukins, or arachidonic acid metabolites, escape regulatory control, they can lead to deleterious host responses that culminate in the septic response and MOF. Thus, although inflammation aids the host at the tissue level, systemic activation can represent a major potential host liability. This hypothesis, that MOF and distant organ injury are related to an uncontrolled or persistent systemic inflammatory state, is consistent with the autopsy study of Nuytinck and coworkers,[57] who found an association between the presence of ARDS or MOF and histologic evidence of organ inflammation.

TABLE 3. *Consequences of Cytokine Insufficiency or Excess*

Cytokine Insufficiency	Cytokine Excess
Impaired wound healing	Local tissue destruction
Increased susceptibility and decreased resistance to infection	Microvascular injury (capillary leak)
Impaired metabolic response to injury	Excessive hypermetabolism (cachexia)
	Hemodynamic insufficiency culminating in a refractory shock state

TABLE 4. *Factors Complicating the Understanding of Cytokine Effects*

1. One cytokine often causes secretion of second or additional cytokines (cytokine cascade).
2. Individual cytokines can modulate the action of other cytokines on the same cell.
3. The physiologic state of the cytokine-producing cell (primed *vs.* tolerant) can influence which cytokines are liberated.
4. Combinations of cytokines can be mutually inhibitory, additive, synergistic, or even result in novel effects not seen with individual cytokine.
5. Sequence of cytokine exposure can influence target cell response.
6. Cytokine effects may be dose-related with qualitatively different biologic effects seen at different doses.

Support for this hypothesis is based on the recognition that macrophage activation and cytokine release can produce a syndrome practically indistinguishable from the systemic response to severe infection. Studies of natural and recombinant cytokines document that most cytokines are pleiotropic and have multiple diverse biologic activities.[55,58] For example, depending on the cell type of the target cell or the environment in which the cytokine is acting, a single cytokine may act as either a positive or negative signal. Therefore, as outlined in Table 4, understanding cytokine effects is complicated, because the precise biologic effect of a cytokine can vary depending on the exact clinical or experimental circumstances in which it is measured. Thus, it is now clear that certain cytokines also have profound effects on intermediary metabolism, substrate mobilization, wound healing, and the cardiovascular system, although originally it was believed that the primary role of cytokines was in immunologic homeostasis.[55,56,58,59]

The cytokine family of proteins includes interleukins (IL), interferons (INF), colony-stimulating factors, and TNF. I will concentrate on IL-1, IL-6, TNF-α, and INF-γ, because these cytokines have been well-studied and appear to be involved or associated with infection, inflammation, and the evolution of MOF. These four cytokines share many common effects (Table 5), and when injected into animals or humans produce many of the systemic, immunologic, and metabolic signs associated with the septic response.[31,32,55–59] Elevated circulating levels of all four cytokines have been detected in the serum

TABLE 5. *Currently Identified Biologic Activities*

Biologic Activity	IL-1	IL-2	TNF-σ	INF-γ
Activate macrophages	Yes	—	Yes	Yes
Activate neutrophils	Yes	—	Yes	Yes
Activate endothelial cells	Yes	—	Yes	Yes
Induce fever	Yes	Yes	Yes	Yes
Induce acute phase response	Yes	Yes	Yes	Yes
Exhibit metabolic effects	Yes	—	Yes	—
Stimulate wound healing	Yes	—	Yes	—

of patients with infectious conditions,[60–68] and TNF and IL-6 have been detected in infected and noninfected burn patients.[69–71] Elevated cytokine levels have been documented also in inflammatory and noninflammatory states in the absence of infection.[72–77]

Based on primate studies and studies in human volunteers and tumor-bearing patients, TNF rather than IL-1 or IL-6 appears to be the messenger that initiates and orchestrates the septic response.[31,32,78–81] This conclusion is based on the following observations: (1) After an endotoxin (human) or bacterial challenge (primate), TNF levels rise and peak well before other potential mediators, including IL-1 or IL-6. (2) The administration of monoclonal antibodies against TNF improves survival and attenuates the expected increase in IL-1 and IL-6 in lethal bacteremic models. (3) The administration of TNF and endotoxin induce similar metabolic responses in humans. (4) Tumor necrosis factor administration mimics the response to injury. In fact, TNF is capable of inducing a whole cascade of secondary factors that can modulate multiple homeostatic systems. A partial list of TNF-inducible factors includes other cytokines, growth factors, endocrine hormones, acute phase proteins, eicosanoids, and endothelial factors.[82]

The frequency of cytokine detection and the clinical significance of cytokinemia has varied from series to series,[60–71] making it difficult to draw definitive clinical or mechanistic conclusions on their role in organ failure or outcome. This failure to consistently and reproducibly identify elevated cytokine levels in critically ill, infected, and septic-appearing patients has been one of the major factors limiting acceptance of the macrophage hypothesis of MOF. Nonetheless, based on controlled human and animal experiments,[31,32,55,78–81] there are several potential physiologic explanations that help explain these inconsistent clinical results. First, because the half-lifes of TNF and the other cytokines in the circulation are very short (minutes), random blood sampling may miss the peaks of activity. Secondly, because TNF is present in the circulation only briefly during the earliest phase of the critical illness or infection, samples taken once the disease process is established may be too late. Lastly, circulating levels of cytokines, especially TNF and IL-1α, may be misleading and may not reflect their tissue levels or biologic activity. That is, cytokines are usually produced and exert their biologic effects locally within organs and tissues and thereby function primarily as paracrine (cell–cell) or autocrine mediators rather than endocrine mediators. Cells of nonmyeloid origin can produce cytokines as well as myeloid cells. For example, endothelial cells produce TNF, IL-1, and IL-6, whereas keratinocytes and epithelial cells produce IL-1 and IL-6. This fact, that multiple diverse nonmotile cell types as well as fixed tissue macrophages can produce cytokines *in vivo* further suggests that cytokines function as paracrine signals that potentially exert important local influences on neighboring parenchymal cells, such as hepatocytes, enterocytes, or alveolar cells. Consistent with this observation is the recent discovery of cell-associated forms of TNF and IL-1α that may differ from those found in the circulation.[55,56,58] Thus, although most clinical studies investigating the role of cytokines in injury and infection have measured circulating cytokine levels, the concentrations of these proteins in the tissues are more likely to be of clinical and biologic importance.

It is also important to remember that the toxicity of TNF, as well as other cytokines, is synergistically enhanced by other factors.[82] For example, IL-1 by itself, even when administered at high doses, is minimally toxic, yet when coadministered with normally nontoxic doses of TNF, the combination becomes lethal. Endotoxin also potentiates the toxicity of TNF, such that the simultaneous administration of individually innocuous doses of endotoxin plus TNF induces a rapidly fatal shock syndrome. Other cytokines, such as platelet-activating factor, IL-6, and INF-γ increase TNF toxicity, whereas transforming growth factor-β attenuates TNF toxicity.[82] These complex cytokine interactions further limit the clinical utility of random blood cytokine level measurements.

Undoubtably, as more basic and clinical information on macrophage and cytokine biology emerges, their precise role in the critically ill patient will be better defined. Nonetheless, it seems clear that cytokines in conjunction with the neuroendocrine axis play a major role in the metabolic response to injury and in the transition from hypermetabolism to organ dysfunction and MOF. Consequently, if MOF represents the terminal phase of the hypermetabolic response, as proposed by Cerra and others,[83] then it should be possible to decrease the incidence of MOF by limiting the development of an uncontrolled systemic inflammatory-hypermetabolic state. Based on the elegant clinical studies of multitrauma patients carried out by Border et al.,.[39] Seibel et al.,[84] and others,[85–87] this appears to be the case. That is, these investigators documented that the institution of a policy of early operative fixation of long-bone fractures, rather than traction fixation, reduces the incidence of ARDS and MOF as well as

shortens the numbers of days on the ventilator and in the intensive care unit (ICU). These clinical studies on the early and definitive fixation of fractures support the hypothesis that, by preventing progressive macrophage activation and thereby limiting the systemic inflammatory response, early and complete successful management of major trauma improves outcome.

Microcirculatory Hypothesis of MOF

In its broadest sense, the microcirculatory hypothesis of MOF proposes that organ injury is related to ischemia or vascular endothelial injury. In this context, the microcirculatory hypothesis of MOF includes several distinct but to some extent overlapping potential mechanisms of injury, including inadequate tissue and cellular oxygen delivery,[53,88,89] the ischemia–reperfusion phenomenon,[90,91] and tissue injury due to endothelial–leukocyte interactions.[48,92] There are many points where the microcirculatory and macrophage hypotheses of organ failure overlap and interact.[92,93] For example, clinical and experimental observations clearly document that systemic inflammation adversely affects the microcirculation, whereas ischemia can exaggerate the host's inflammatory response to subsequent stimuli by activating neutrophils and priming macrophages.

Intermediary metabolism and energy production have an absolute dependence on oxygen, and oxygen cannot be stored intracellularly. Thus, regardless of the cause, inadequate oxygen availability rapidly leads to cellular dysfunction, injury, and ultimately cell death, with the net result being organ dysfunction. Because the role of inadequate oxygen availability in the pathogenesis of tissue and cellular injury is well established, it is not difficult to conceptualize how periods of prolonged hypotension or organ ischemia can lead to organ injury. In addition to decreased tissue perfusion, however, circulatory shock is associated with distinct changes in the microcirculation, which include vascular congestion and sludging, the formation of microthrombi composed of leukocyte and platelet aggregates, interstitial edema, and increased capillary permeability.[94]

Although the cellular events that occur during hypotension and ischemia are well recognized to contribute to the pathogenesis of organ injury, the role of reperfusion in this process has only recently been appreciated.[90,91] As illustrated in Figure 2, the re-establishment of blood flow after ischemia can itself cause tissue injury. During the period of ischemia, energy stores are depleted because of the continuing energetic demands to maintain cellular homeostasis and a reduced capacity to regenerate adenosine triphosphate by oxidative phosphorylation. Although ischemia-induced tissue hypoxia can lead to irreversible tissue injury if the period of ischemia is sufficiently prolonged, frequently much of the tissue damage occurs after oxygenation is restored rather than during the period of ischemia. Thus, although reperfusion is necessary for the restoration of metabolic activity, it can induce or aggravate the extent of ischemic tissue injury. In this context, hemorrhagic shock or any disease process that causes systemic hypotension can be viewed as causing a global ischemia–reperfusion syndrome.

There are several important biologic sources of oxygen radicals, including xanthine oxidase, activated leukocytes, mitochondria, prostaglandin synthetase, and catecholamine auto-oxidation, but xanthine oxidase and leukocytes appear to be the major sources in clinical disease states.[90,91] Although unproven, the fact that the conversion

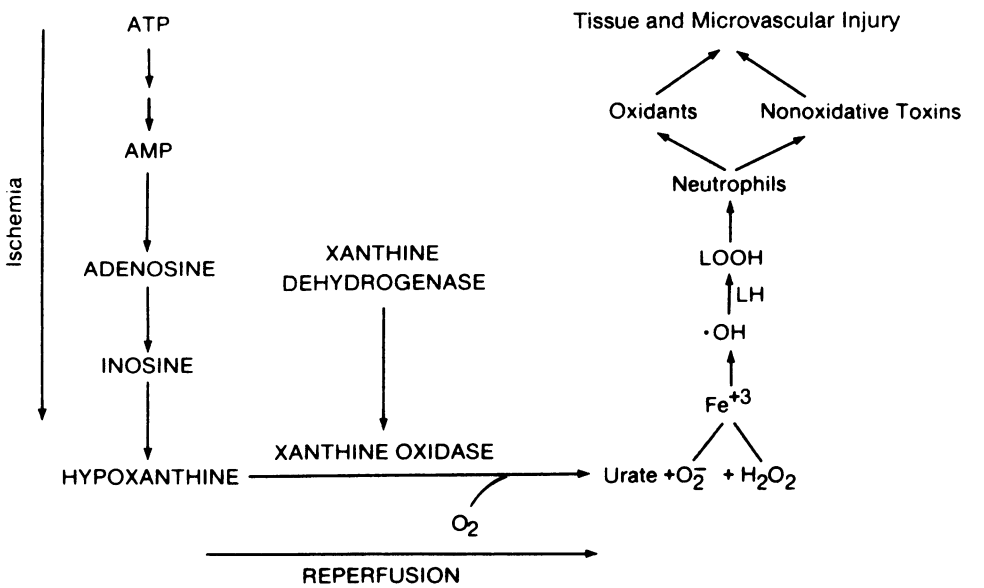

FIG. 2. The proposed pathway by which the ischemia–reperfusion phenomenon results in microvascular and tissue injury. The process begins with tissue ischemia and the consequent production of hypoxanthine from adenosine triphosphate and the conversion of xanthine dehydrogenase to xanthine oxidase. On reperfusion, oxygen radicals are formed from O_2 by the enzymatic action of xanthine oxidase. These oxidants in combination with recruited neutrophils lead to endothelial and tissue injury.

of xanthine dehydrogenase to xanthine oxidase takes only 10 seconds in intestinal tissue, 8 minutes in cardiac muscle, and about 30 minutes in the liver spleen, kidney, and lung[95] may help explain the differential relative susceptibility of these organs to ischemia–reperfusion-mediated tissue injury.

Basic studies of endothelial cell physiology and function clearly indicate that endothelial cells are active participants in the regulation of blood flow,[96] coagulation, and inflammation.[48,92,93] It is in this role as regulators of coagulation and inflammation that endothelial cells, in conjunction with circulating neutrophils, appear to promote tissue ischemia and injury. Endothelial–leukocyte interactions resulting in tissue injury appear to be a common pathway by which a diverse number of initiating factors, such as bacteria, endotoxin, cytokines, and ischemia can lead to organ failure and MOF. For example, endotoxin, TNF, IL-1, and to a lesser extent other cytokines induce a change in endothelial phenotype from a noninflammatory to a proinflammatory, procoagulant phenotype.[93] These activated proinflammatory endothelial cells have lost their anticoagulant properties and now express tissue factor and acquire the capacity to bind factor VIIa and thus activate the extrinsic clotting pathway. Additionally, these proinflammatory endothelial cells now express surface receptors (ELAM-1, ICAM-1) that promote leukocyte adherence and secrete leukocyte-activating factors, such as IL-1, platelet-activating factor, IL-8, mitotic-control protein-1, GM-CSF, and G-CSF. This shift in endothelial phenotype ultimately results in focal microvascular thrombosis and leukocyte-mediated endothelial injury. If widespread, this phenomenon can progress to tissue ischemia and ultimately organ failure. Conversely, cytokine induction of a proinflammatory endothelial cell phenotype is of distinct host benefit in the control and eradication of bacterial invaders. For example, at foci of bacterial invasion, endotoxin or inflammatory cytokines induce endothelial cell ELAM-1 expression, and by binding to circulating neutrophils ELAM-1 recruits them to the inflammatory site. In this situation, the activated endothelial cells serve as messengers that signal circulating neutrophils for help.

In this scheme, neutrophil adherence to endothelial cells is a prerequisite for endothelial and subsequent tissue injury. If this hypothesis is correct, it should be possible to prevent or limit tissue injury by preventing neutrophil adhesion. Because neutrophil adherence to endothelial cells is mediated to a large extent by the binding of the neutrophil membrane–glyocprotein complex CD11/CD18 to the endothelial adhesion molecules ELAM-1 and ICAM-1, this hypothesis can be tested using anti-CD18,[97–99] anti–ICAM-1, or anti–ELAM-1 antibodies.[100,101] These and other experimental studies[102] document that shock or ischemia–reperfusion-mediated endothelial cell and organ injury can be ameliorated by preventing neutrophil adhesion to endothelial cells. Thus, although not fully proven and as yet untested clinically, the experimental evidence generated to date is consistent with the concept that systemic processes, such as ischemic, inflammatory, or infectious insults, which injure or activate endothelial cells, can ultimate lead to microvascular-mediated organ injury.

Clinical observations supporting the microcirculatory hypothesis of organ injury include the following observations: (1) Circulatory shock with resultant tissue hypoxia is one of the most common clinical events preceding MOF. (2) There is autopsy evidence of diffuse microvascular injury in patients with MOF.[57] (3) Neutrophils, platelets, and fibrin are characteristically found in the pulmonary microcirculation of patients with ARDS.[103] (4) The results of hemodynamic studies in patients with ARDS or MOF indicate that oxygen delivery is not sufficient to meet oxygen demands.[104] This hypothesis of MOF can theoretically explain the clinical paradox of why identification and appropriate treatment of an infectious focus fails to improve survival in some patients, because once the microcirculatory inflammatory/injury process is sufficiently established, removal of the initiating or perpetuating stimuli will not rapidly reverse or even prevent further tissue injury, organ failure, or death.

Gut Hypothesis of MOF

In this hypothesis, intestinally derived bacteria or endotoxin serve as triggers to initiate, perpetuate, or exacerbate the septic state and thereby promote the development of MOF. The gut, macrophage, and microcirculatory hypotheses of MOF clearly overlap, because bacteria and endotoxin efficiently induce cytokine secretion by resident tissue macrophages, promote a proinflammatory endothelial cell phenotype, stimulate neutrophil protease and oxidant production, and activate multiple humoral protein cascades, including the complement and coagulation systems. Once this cycle is initiated, theoretically it can become self-sustaining. For example, the products of endotoxin-activated macrophages (*i.e.*, IL-1, IL-6, TNF, prostaglandin E_2 [PGE_2]), neutrophils, and plasma protein cascades in conjunction with endothelial cells can impair oxygen delivery to the gut through their effects on the microcirculation, and by increasing intestinal permeability potentiate the further translocation of intestinal endotoxin. The general phenomenon of the loss of intestinal barrier function leading to the systemic spread of bacteria or endotoxin has been termed bacterial translocation.[105,106]

One clinically attractive aspect of the gut hypothesis is that bacterial translocation would explain the apparent paradox of why no septic focus can be identified clinically or at autopsy in more than 30% of bacteremic MOF patients dying with clinical sepsis.[25] A second component

of this hypothesis is that the presence of gut-derived portal or systemic endotoxemia may be the signal that triggers, perpetuates, or exacerbates the hypermetabolic and immunoinflammatory responses and thereby contributes to the development of a septic state in patients without evidence of infection. Thus, the gut hypothesis of MOF clarifies how patients can develop enteric bacteremias in the absence of an identifiable focus of infection or develop a septic state in the absence of microbiologic evidence of infection.

The hypothesis that the gut can be the reservoir for bacteria causing systemic infections is supported by several lines of evidence. First, there is experimental evidence from many laboratories, including my own, documenting that intestinal bacteria can escape from the gut and cause systemic or peritoneal infections.[42,107-109] Secondly, the mucosal barrier to bacteria appears to be lost under certain clinical circumstances, resulting in systemic infections. For example, life-threatening infections with gut-associated bacteria in which no infectious focus could be found has been documented in burn patients,[110] victims of trauma,[39,111] and patients developing the multiple organ failure syndrome.[25] The clinical recognition that the gut may be a reservoir for bacteria causing systemic infections in critically ill ICU patients led Border and co-workers[39] to coin the term "gut septic states" to describe this phenomenon; the recognition that gut failure and distant organ failure may be casually related prompted Meakins to propose that the gut was the "motor" of MOF.[112]

Although bacterial translocation can be induced in a variety of animal models and by very different insults, experimental studies on the pathophysiology of bacterial translocation and gut barrier failure indicate that one or more of three basic pathophysiologic conditions are necessary for bacterial translocation to occur.[109] These are: (1) disruption of the ecologic balance of the normal indigenous microflora, resulting in bacterial overgrowth with gram-negative enteric bacilli, (2) impaired host immune defenses, and (3) physical or functional loss of the mucosal barrier. These conditions are commonly observed in the critically ill or injured patient at risk of developing enteric bacteremias or MOF. These patients frequently have experienced major blood loss or a hypotensive episode, which may injure the gut mucosa; they are frequently immunocompromised and the antibiotic regimens they receive may disrupt the normal ecology of the gut flora, resulting in colonization with exogenous pathogens.[113] In addition, therapeutic regimens, such as gastric acid neutralization for stress ulcer prophylaxis, may result in the colonization of the stomach and distal intestine with potential pathogens.[114] Hyperosmolar enteral or parenteral feedings may disrupt not only the normal bacterial ecology of the gut, but also may result in mucosal atrophy and altered intestinal mechanical defenses.[115,116] The hypoalbuminemia and capillary leak syndrome that commonly occur in these patients can result in intestinal edema, impaired jejunoileal peristalsis, intestinal stasis, bacterial overgrowth, and increased intestinal permeability. Thus, these and other changes can easily be seen to promote the failure of the gut barrier to bacteria and endotoxin, and are consistent with recent clinical studies documenting that intestinal permeability is increased during sepsis,[117] shortly after thermal injury,[118] or in healthy volunteers receiving a single dose of endotoxin.[119] Although these and other studies indicate that intestinal permeability is increased in a variety of clinical and experimental circumstances, conflicting data are available on whether intestinal barrier function is[120] or is not lost[121] in trauma victims.

Because life-threatening infections can originate from the gut, several groups of investigators have attempted to reduce the incidence of systemic infections in high-risk patients by orally administering nonabsorbable antibiotics (in some cases with systemic antibiotics) directed against gram-negative enteric bacilli and *Candida.* This process is termed "selective gut decontamination."[122] In selective gut decontamination, preservation of the anaerobic intestinal flora is important, because loss of the anaerobes is associated with intestinal overgrowth by gram-negative enteric bacilli, *Pseudomonas* species, and *Candida.* The results of these clinical studies are encouraging, because selective gut decontamination reduces the incidence of pneumonias, primary bacteremias, and other infectious complications by about 50%.[123] The clinical efficacy of selective decontamination in high-risk patients remains controversial, however, because most studies have not documented an improvement in survival in spite of this reduction in the rate of infection.[123] The failure of selective gut decontamination to improve survival raises questions about the clinical relevance of gut barrier failure and even traditional infection to outcome in critically ill ICU patients.

In some ways, it is not surprising that attempts to control the gut flora do not increase survival, because the patients enrolled in these studies are almost always profoundly immunocompromised and their intestinal barrier function is lost to endotoxin as well as bacteria. What this means clinically is that selective decontamination of the gut microflora is unlikely to be fully effective in preventing gut-origin septic states in patients with a damaged intestinal mucosa or profound immune suppression. This concept is consistent with experimental studies indicating that after hemorrhagic shock, burns, or endotoxin challenge, the physical barrier function of the intestinal mucosa appears to be of primary importance in preventing or limiting the escape of bacteria or endotoxin.[41,51,124] Furthermore, because mucosal injury and bacterial translocation can be prevented in these three clinically relevant

models, by blocking xanthine oxidase-generated oxidants, it appears that a common pathway of mucosal injury involving an ischemia–reperfusion mechanism may be involved. Thus, as will be discussed in the concluding section on therapy, more is required to prevent the translocation of bacteria and endotoxin than just the maintenance of a normal gut microflora.

Lastly, based on a series of *in vivo* and *in vitro* studies, it appears that a clinically important relationship may exist between the state of intestinal barrier function, Kupffer cell function, the hypermetabolic response, and distant organ injury.[43,83,125,126] That is, gut-derived endotoxin may regulate Kupffer cell activity and the subsequent release of endogenous mediators that modulate hepatocyte function. Additionally, because the hepatic reticuloendothelial system (Kupffer cell) appears to play a role in the clearance of translocating bacteria or endotoxin from the portal circulation, impaired hepatic reticuloendothelial system activity may potentiate the systemic effects of gut barrier failure by allowing gut-derived bacteria or endotoxin to reach the systemic circulation, where they will fuel the septic response.

Two-hit Phenomenon in MOF

The phrase "two-hit phenomenon in MOF" is used to describe the biologic phenomenon in which an initial insult primes the host such that on a second or subsequent insults, the host's response is greatly amplified. My own bias is that this biologic phenomenon plays a major role in the pathogenesis of MOF and thus warrants specific discussion. For example, in the polytrauma patient, an episode of hypotension by decreasing blood flow to various organs could produce a mild (clinically undetectable) focal or global ischemia–reperfusion injury as well as hypoxia-mediated priming of resident macrophages and neutrophils, thereby resulting in tissue inflammation. Any subsequent insult, such as infection, then would lead to an amplified tissue response manifested as increased macrophage cytokine production, neutrophil oxidant release, and microcirculatory disturbances. Because the gut appears to be particularly sensitive to ischemia–reperfusion-mediated injury, early failure of intestinal barrier function may further contribute to this process by amplifying the magnitude of the systemic inflammatory signal. In this light, it appears that an inflammatory stimulus may not need to be overwhelming, just persistently greater than the host's ability to clear it to promote MOF.

In this paradigm, shock leading to tissue ischemia primes the host for an exaggerated response to subsequent insults such as bacteria or endotoxin. Other potential physiologic primers besides tissue ischemia include significant tissue injury or bacteria that induce a systemic inflammatory state. Additionally, the same factors that prime the host can serve also as secondary or subsequent stimulatory signals. Furthermore, the magnitude of a stimulus required to prime macrophages or neutrophils is only one-tenth to one-hundredth the amount necessary to activate these cells.[127] Although unproven clinically, it is well recognized experimentally that a large number of physiologic insults, such as shock, mechanical trauma, or burn injury, will prime the host to the extent that otherwise nonlethal bacterial or endotoxin challenges become lethal.[128] This is not to say that all patients developing MOF follow this paradigm, because clearly MOF can develop after a single, clinically definable insult if it is sufficiently severe.

Therapy

General Concepts

The best treatment for MOF is prevention. Because infection, inadequate tissue perfusion, and a persistent inflammatory state are the commonest and most important risk factors for the development of MOF, it seems logical that our initial therapeutic efforts should be directed at their early treatment or prevention. Prevention takes different forms in different patients. For example, in trauma victims, Border and co-workers[39] and Seibel et al.[84] have presented compelling evidence that immediate definitive treatment of all injuries, including long bone fractures, is effective in preventing ARDS and MOF. The basic concept behind this approach is that immediate treatment of all treatable injuries is the best way to shut down or limit the inflammatory response and thereby restore a more normal physiologic state. Similarly, early definitive primary or reoperative surgery leading to the removal of necrotic tissue, the drainage of abscesses, and the control of peritoneal soilage may be effective in the nontrauma patient.

Not only is there increasing evidence that inadequate oxygen delivery may play a role in the development or perpetuation of organ failure, but it is equally clear that the presence of a normal or even increased cardiac output does not ensure that sufficient oxygen is being delivered to the tissues to meet their metabolic needs.[129–132] Under normal circumstances, even moderate decreases in oxygen delivery or increases in tissue oxygen demands (hypermetabolism) can be compensated for by an increase in the amount of oxygen extracted from the blood. The term "supply-independent oxygen consumption" is used to describe this normal physiologic relationship, where oxygen consumption is independent of oxygen delivery. In patients with sepsis, ARDS, or MOF, however, oxygen consumption appears to be supply dependent even when cardiac output and total body oxygen delivery are supranormal. This relative failure of oxygen delivery is termed "pathologic supply-dependent oxygen delivery" and ap-

pears to be due to a maldistribution of perfusion at both the organ and microcirculatory levels.[53,129-132] The net result is that some tissues are overperfused while others are underperfused, resulting in patchy areas of organ injury. Because most evidence indicates that oxygen delivery becomes supply dependent at some point in patients with ARDS or MOF,[104,129,131] and that, in this situation, the delivery of supranormal amounts of oxygen improves survival,[88,104,130,132] it appears prudent to optimize oxygen delivery in all high-risk patients. The best way to ensure that oxygen consumption is not supply dependent is to make serial measurements of oxygen consumption as oxygen delivery is increased.[104,129,131] Based on extensive studies in high-risk surgical patients, it appears that survival can be improved by maintaining the cardiac index at or above 4.5 L/minute/m^2, oxygen delivery at 600 mL/minute/m^2, and oxygen consumption at 170 mL/minute/m^2.[88,130,132]

The role of total body as well as organ-specific nutritional support in the prevention and therapy of MOF has received increasing attention over the last decade. It is now well recognized that there is a continuum of metabolic alterations through which these patients pass as they progress from uncomplicated trauma through the sepsis syndrome to frank MOF, with the end result being a hyperglycemic, hypermetabolic, immunocompromised catabolic patient with marked muscle wasting and organ failure. In contrast to unstressed humans, where intermediary metabolism is primarily under neuroendocrine control, in septic humans, the mediators of the hypermetabolic response include proinflammatory factors, such as the macrophage products IL-1, IL-6, and TNF, as well as the traditional neuroendocrine mediators.[133] One practical consequence of this new metabolic information is the realization that the appropriate nutritional approach to the patient with sepsis or MOF must differ from that in healthy humans. Although controversy still exists over the optimal nutrient mix for the individual patient, it is clear that patients with or at risk of developing MOF require higher levels of energetic substrates (calories) as well as protein. Although both the amounts of calories and protein required to meet the metabolic demands of these patients are increased, relatively more protein than calories is required.[134] Thus, the optimal nonprotein calorie: nitrogen ratio is lower in the critically ill patient (100:1) than in healthy humans (150:1), and the amount of protein administered daily is higher (1.5 to 2.5 g/kg *versus* 1 g/kg).

The route of nutrient delivery also appears to be important; there is increasing clinical and experimental evidence indicating that enteral alimentation is physiologically superior to parenteral alimentation. This beneficial role of enteral feeding has received increasing attention since Kudsk et al.[135] documented that animals fed enterally survive a septic insult better than animals fed an identical diet parenterally. In a prospective study where burned children were randomized to receive their nutritional support either parenterally or enterally, Alexander et al.[136] conclusively demonstrated that high-protein enteral feedings improved systemic immunity, reduced the incidence of infections, and most importantly, increased survival. Similarly, in a prospective randomized clinical trial, Moore et al.[137] documented that enterally fed trauma victims had fewer infectious complications than parenterally fed patients. In contrast to these clinical trials, Cerra et al.[138] did not find that enteral feeding was effective in preventing MOF in patients with sepsis. Because the patients in Cerra's study did not receive enteral feedings until an average of 5 days *after* the onset of their illness, however, the enteral feedings appear to have been started too late to be effective. In addition to these clinical studies, early enteral feeding has been experimentally documented to bolster antibacterial host defenses,[135] blunt the hypermetabolic response to trauma,[126] maintain mucosal mass and barrier function, and to limit or prevent disruption of the normal gut microflora.[115,116,139]

The exact reasons why enteral feedings appear physiologically superior to parenteral feedings in maintaining intestinal barrier function, mucosal mass, and host immune function are not fully known. Wilmore et al.[116] recently reviewed the concept that gut barrier failure may occur in critically ill patients, at least in part, because current methods of parenteral nutrition do not fully support intestinal structure and function. That is, normal enterocyte growth and repair requires specific nutrients, such as glutamine,[116,140] which are not present in current intravenous amino acid solutions. Because loss of intestinal barrier function can lead to the translocation of bacteria and endotoxin, which can fuel the septic response, means of preventing, limiting, or speeding the repair of acquired intestinal mucosal injury that frequently occurs after shock, sepsis, or trauma are required. For this reason, investigations testing the ability of specific nutrients, such as glutamine[116,140] or short-chain fatty acids,[141] growth factors,[142] trophic gut hormones,[143,144] intraluminal bulk,[115] as well as immediate enteral feeding to prevent or limit gut atrophy or injury, are being performed. Thus, in the future, the optimal therapy to maintain or restore intestinal mucosal structure and function may be a combination of specific enterally administered nutrients and mucosal trophic factors. In fact, as we learn more about the basic biology of the metabolic response to injury, the more likely it appears that specific nutrients will be used to modulate the inflammatory and immune systems to the advantage of the patient.[145,146] Until then, although it is frequently impossible to administer all the required nu-

trients enterally, the gut should be used as soon as possible to deliver at least a portion of the patient's needs.[147] On a practical level, this means that many patients, at some time, will be receiving nutrients by both enteral and parenteral routes.

Hypothesis-driven Potential Therapy

Treatments such as artificial ventilation or hemodialysis are important in prolonging survival in MOF patients with established end stage organ failure. Overall, however, these largely palliative therapeutic efforts do little to improve survival or reverse the underlying processes leading to or perpetuating organ failure. For these reasons and because organ-directed therapy has been reviewed elsewhere,[1-3] purely organ-specific therapies will not be discussed. Instead, I will concentrate on potential therapeutic approaches directed against the potential initiators, systemic mediators, potentiators, and effectors of injury in this syndrome.

As previously discussed, there are four major, and to some extent overlapping, hypotheses proposed to explain various aspects of the pathophysiology of MOF. These are (1) the infection hypothesis, (2) macrophage-cytokine hypothesis, (3) microcirculatory hypotheses, and (4) the gut hypothesis. Based on the pathophysiology that underlie these hypotheses, there are multiple potential sites at which we can intervene to modulate the system in favor of the host. For example, in the infection and gut hypotheses, bacteria and endotoxin are the triggers that initiate an overexuberant inflammatory response, which ultimately leads to organ injuy. Mediators of injury in this paradigm include macrophage products, activated neutrophils, and various humoral factors such as complement and coagulant products. These and other mediators induce a proinflammatory endothelial cell phenotype as well as promote microcirculatory dysregulation. The net result is endothelial cell injury and microvascular thrombosis, which results in a capillary leak syndrome and patchy areas of decreased tissue perfusion. Potentiators of this process include inadequate oxygen delivery to meet tissue demands and the presence of injured or necrotic tissue, which exacerbate the inflammatory response. The critically important therapeutic roles of definitive early surgery, optimization of oxygen delivery, and nutritional support as means of limiting these potentiating factors was covered above and will not be further discussed.

As illustrated in Table 6, using the example of bacteria or endotoxin as the initiators or perpetuators of MOF, this process can be and is being attacked at the initiator, systemic mediator, effector, or tissue levels. For example, two prospective randomized trials employing different monoclonal antibodies against endotoxin have been recently published, documenting that survival can be improved in subgroups of patients with sepsis.[148,149] Therapy directed against endotoxin is biologically attractive for several reasons. First, endotoxin is capable of initiating the cascade of physiologic events that culminate in organ failure. Secondly, in some clinical series,[150,151] the presence of endotoxemia was a more accurate indicator of sepsis, ARDS, or septic shock than were positive blood cultures. Lastly, clinical[152] and experimental[153] studies document that plasma endotoxin levels can rise significantly after the systemic administration of antibiotics because of the release of endotoxin from bacterial cells. In this context, it is possible that antibiotic-mediated bacterial lysis may liberate larger amounts of circulating endotoxin than can be rapidly cleared by the liver, thereby resulting in exacerbation of the inflammatory response. Because survival in bacteremic or infected patients with ARDS or MOF is often not improved despite adequate antimicrobial therapy, it is possible that anti-endotoxin therapy in conjunction with antimicrobial agents may improve survival in some patients with gram-negative sepsis by shutting down or controlling the septic response.

TABLE 6. *Potential Therapeutic Strategies*

Level of Intervention	Factor	Strategy
Initiator	Endotoxin	Antibody-mediated neutralization
Mediator	TNF	Antibody-mediated neutralization
	IL-1	Target cell receptor blockade
Effector	Neutrophils	Antiadherence (CD 11/18) monoclonal antibodies, antioxidants
	XO-generated oxidants	Antioxidants, inhibitors/ inactivators of XO
Tissue level	Endothelial cell	Anti-Elam-1 or anti-ICAM-1 antibodies

XO, xanthine oxidase.

Because TNF and IL-1 appear to be major proximal mediators of the septic response, the use of specific antibodies to block or neutralize these substances would be a second site of potential therapeutic intervention. As previously discussed, administration of antibodies against TNFα improves survival in primates and other mammalian species challenged with otherwise lethal doses of bacteria or endotoxin.[79,82,154] The results of a phase 1 study, in which 14 patients with septic shock received recombinant anti-TNF antibodies, was encouraging in that these antibodies improved arterial blood pressure and no adverse reactions were observed.[155] Advantages of anti-TNF antibodies are that they are likely to be effective in patients with gram-positive infections or nonbacterial inflammatory states associated with macrophage overactiv-

ity, as well as in patients with gram-negative infections. Because, however, in experimental studies, anti-TNF antibodies must be given either before or shortly after (minutes) the insult to be effective, it is likely that this narrow temporal window of effectiveness will limit their clinical utility. A second therapeutic strategy is to block the receptor on the target cells to which the cytokine binds. This approach appears feasible, based on experimental studies with a newly discovery and recently cloned member of the IL-1 cytokine family, termed IL-1 receptor antagonist (IL-1ra).[156–158] Because IL-1ra binds to the IL-1 receptor on various target cells but has no agonist activity, this cytokine functions as a naturally occurring specific receptor antagonist. The use of a receptor blocker is appealing, because it is likely to be effective in dampening the host's response to both infectious and inflammatory insults. One major potential problem with therapy directed against these two cytokines, however, as well as other proinflammatory mediators, is that under normal physiologic conditions both TNF and IL-1 play important roles in the eradication of invading bacteria, in wound healing, and in metabolic homeostasis.[55,56,58,59] In fact, recent studies document that, although the administration of large doses of cytokines are deleterious, when given at low or moderate doses these same cytokines improve survival after endotoxin or bacterial challenge.[159–161] Because controlled clinical trials employing anti-TNF antibodies or the recombinant IL-1ra are underway in patients with sepsis, more information on their clinical utility should be forthcoming.

At the microvascular and tissue levels, therapy directed at specific effectors of tissue injury, such as neutrophil oxidants and proteases or xanthine-oxidase–generated oxidants, is potentially feasible, as is therapy directed at preventing or limiting neutrophil–endothelial interactions.[41,97–102] Additionally, a number of other adjuvant therapies, including cyclooxygenase blockade,[162,163] calcium channel antagonists,[164] and immunomodulators, such as INF-γ,[165,166] GM-CSF,[167] thymopentin,[168] and platelet-activating factor antagonists,[169] are currently in various stages of investigation. These agents have either not been adequately tested clinically or the results of clinical trials are controversial. Lastly, based on prospective randomized studies, it is clear that certain therapeutic modalities are not beneficial in the treatment of patients with severe infections or septic shock. These include the opioid antagonist naloxone,[170] plasma fibronectin repletion,[171] and steroids.[172,173] Not only are steroids not indicated in the treatment of septic shock, because they do not improve survival, but in some of the patient subgroups (those with renal failure), steroid therapy actually increases mortality rates.

Thus, based on our knowledge of the biology of the sepsis syndrome and the preliminary results of clinical trials using various agents to block specific mediators involved in the septic response, it is not unlikely that, in the future, treatment of the septic patient will be similar to that of the patient with cancer, where multiple agents with different actions are combined to produce the desired biologic effect. Thus, one major challenge for the future will be to identify ways of blocking the deleterious effects of cytokines and other mediators of the inflammatory response while maintaining their beneficial effects.

Conclusion

The goal of this review has been to summarize and put into perspective a portion of the enormous amount of clinical and experimental information generated during the last decade on the pathophysiology and potential therapy of MOF. This subject has been characterized by controversy, confusion, and conflicting data, since its initial description in the 1970s. Our attempts to resolve these very opposing thoughts, conflicting experimental and clinical data, and contradictory theories, however, have led to major advances in the understanding of the basic biology of injury and inflammation and the development of new therapeutic strategies. Thus, in the future, only as new hypotheses are generated, tested, and when found to be lacking, either modified or rejected, will further progress be made. Because effective therapy is based on sound biology, as we continue to gain a better understanding of the basic mechanisms involved in this syndrome, we undoubtable will develop new and effective therapeutic strategies, to the benefit of our patients.

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