INTRODUCTION

In 1794 John Hunter wrote: “There is a circumstance attending accidental injury which does not belong to disease—namely, that the injury has in all cases a tendency to produce both the disposition and the means of a cure.” This first described the stress response, a biphasic physiologic response that, when uninterrupted by complications, has predictable characteristics and lasts 7 to 10 days. The early phase that occurs immediately following injury is characterized by a hyperinflammatory response with excessive release of mainly proinflammatory cytokines, chemokines, and reactive oxygen species. It lasts roughly for about 24 hours and is followed by a period of immune suppression that characteristically persists for about 5 to 7 days. The driving force for this second phase appears to lie with the need to mount an immune or inflammatory response to combat infection and facilitate repair of damaged tissues. Most markers for ongoing inflammation start to rapidly increase about 8 to 12 hours after the stimulus, and demonstrate peak levels on postinjury day 2, returning to baseline around day 7.

SURGERY, AN ELECTIVE TRAUMA

In the context of host response, there is little difference between accidental and surgical trauma. From a research perspective, the surgical intervention’s projectable timeframe has enabled a better understanding of signaling pathways and mechanistic models. Simultaneously, strategies emerged to attenuate and modulate the overwhelming inflammatory response elicited by major surgery; many of these strategies failed to improve—or even worsened—clinical outcome. This suggests a “janiform” role of the physiologic stress reaction in the body’s management of injury: While harmful if exaggerated, it is mandatory to induce regeneration and preservation strategies.

PATHOPHYSIOLOGY

David P. Cuthbertson was the first to study the host response to injury and in 1929 proposed a paradigm by which the body responded to injury: If the damage to the patient is not immediately fatal, there is a compensatory reaction in which vasoconstriction shunts blood away from the periphery and toward central organs, most notably the heart and brain; this promotes short-term survival. Hypothermia and oliguria are associated with a global decrease in oxygen consumption and energy expenditure; in an effort to expand plasma volume and avoid failed oxygen delivery, the body conserves salt and water by increasing aldosterone secretion (1). These effects are seen throughout the body in the first 24 hours after injury. Cuthbertson termed this sequence of events the “ebb” phase of traumatic shock. When death is not imminent, a second aspect of the response emerges, the key to which is an attempt to repair tissue damage, accomplished via the activity of white blood cells (WBCs). As part of the initial inflammatory response, the release of chemotactic mediators and involvement of the complement cascade trigger the migration of immune cells to the site of inflammation.

The immunologic defense capacity is determined by the functional interplay between the innate and the adaptive immune systems (2). The initial recognition of infectious agents or damage is carried out by the innate immune system; the sensing of pathogens is performed by specialized, sentinel immune cells, which are located in tissues with direct contact to the environment. The interaction between pathogen- and damage-associated molecular patterns (PAMPs/DAMPs) and their receptors results in induction of different signal transduction pathways and the transcription of various genes, which further results in an increased production of inflammatory and immunoregulatory cytokines (2).

As an important contributor to the innate immune system, inflammasomes—cytosolic protein complexes—assemble in response to DAMPs and PAMPs, resulting in the activation of caspase-1 and generation of the proinflammatory cytokines interleukin (IL)-1β and IL-18. The NLRP3 inflammasome is currently the most fully characterized and consists of NLRP3 (NACHT, LRR, and PYD domains-containing protein), ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain), and caspase-1, which is its central effector protein. The inflammasome participates in both physiologic and pathologic inflammatory processes and contributes to several systemic diseases (3–5).

Inflammatory and immunoregulatory cytokines regulate the ensuing cellular and humoral immune response. Mouse strains with deletions in genes encoding cytokines or cytokine receptors show an increased susceptibility to infection (6). The uncontrolled increase of proinflammatory cytokines, in turn, frequently contributes to the development of organ dysfunctions and severe complications in patients with sepsis and septic
shock. Cytokines act by binding cognate receptors expressed on target cells to activate signal transduction pathways, gene transcription, and the expression of downstream effector molecules. Additionally, release of chemoattractant mediators triggers the migration of immune cells, and slowed circulation in the ebb phase allows WBCs to move toward the periphery and adhere to the endothelium. Neutrophils react first, with macrophages following. With restoration of the circulation, the process becomes active. It is characterized by phagocytosis and lysis of bacterial, viral, or fungal invaders, and removal of cellular debris. In addition, macrophages, lymphocytes, and antigen-presenting cells (APCs) secrete cytokines, which serve to further amplify the overall inflammatory response; to a great extent, these are growth factors such as vascular endothelial growth factor (VEGF) that facilitate repair of damaged tissue by stimulating angiogenesis and vasculogenesis.

The process of repair and recovery requires enormous amounts of energy, with a 2- to 20-fold increase in oxygen consumption and resting energy expenditure (REE). In sequence, body temperature rises, and oxygen consumption and carbon dioxide production increase (1,7). Monk et al. showed an increase in REE of up to 55% above predicted in trauma patients (8). Other studies demonstrated that survival is dependent partly on the ability to maintain hypermetabolism and adequate oxygen utilization (7,9–12). Because WBCs are, more or less, obligate glucose users, there is an associated increase in glucose requirements (13). After the first 24 hours, hepatic glycogen stores are depleted and a source of de novo glucose is required; this is generated by hepatic gluconeogenesis. However, adequate mobilization is not enough to ensure substrate delivery. Therefore, the response includes capillary dilatation to increase flow and improve delivery. Unfortunately, due to thrombosis in damaged tissue, most injured areas are avascular. To allow substrate delivery to these regions, capillary tight junctions separate allowing fluid and substrate to “leak” from the vasculature. Increased vascular permeability results in redistribution of extracellular fluid and plasma proteins to form edema and exudate (14). Glucose and other nutrients move down their concentration gradients across the extracellular matrix to areas of damage. Removal of waste requires an increase in renal blood flow and glomerular filtration to enable excretion of amino acid degradation products.

Early studies demonstrated that initiation of the flow phase is, in part, hormonally modulated. An initial, dramatic, release of endogenous catecholamines (15) is supplemented by alterations in the somatotropic system (growth hormone and insulin-like growth factor) such that anabolism is postponed and energy substrates are redirected to vital organs; both the thyroid and the gonadal axes are suppressed. Adrenocorticotropin hormone (ACTH) secretion is heightened by increased corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), catecholamines, angiotensin II, serotonin, and some proinflammatory cytokines (IL-1, IL-2, IL-3, IL-6), tumor necrosis factor (TNF), macrophage migration inhibitory factor (MIF), and anti-inflammatory cytokines, including IL-10 and IL-1RA (16,17). ACTH stimulates the adrenal glands to produce glucocorticoids and mineralocorticoids; glucocorticoids and glucagon promote gluconeogenesis and glycogenolysis and induce peripheral insulin resistance, leading to increased glucose production (18), this, in turn, increases insulin secretion, producing an “insulin-resistant” state.

Hemorrhage and traumatized tissue further contribute to the excessive release of these mediators, which initiates the tissue repair by trafficking immune cells, such as macrophages to the injured tissue. In case of hemorrhage, the coagulation cascade is triggered by both the intrinsic and extrinsic pathways. This also serves to sustain and enhance immune cell migration and activation. In addition, fibroblasts at the edge of the wound divide, migrate toward the center, and produce collagen. New capillaries bud, and the neovascularization further supports the repair and tissue regenerating. Eventually the wound edges will fuse and consist of vascularized granulation tissue; this process is mediated by an increase in fibroblast growth factors, epidermal growth factor, platelet-derived growth factor, and VEGF (19,20).

This massive mobilization of defense mechanisms may also affect normal tissue. Therefore, one of the most important characteristics of the normal stress response is the balance between the inflammatory and the anti-inflammatory systems. This involves the proinflammatory cytokines TNF-α and MIF, which are released by the activated macrophages and various other cell types in response to infection, hypoxia, or harmful stimuli. TNF-α is capable of stimulating the medullary reticular formation and the hypothalamus in the brain; this activation of the hypothalamic–pituitary–adrenal axis ultimately causes increased anti-inflammatory activity. For example, glucocorticoids released as a result of this process limit the negative biologic consequences caused by inflammation (21). TNF-α also stimulates the dorsal vagal complex and alters the efferent vagal output; this is, in part, responsible for “sickness” behavior, such as anorexia and fever (22–24). More importantly, however, is neuromodulation of the immune response. The “inflammatory reflex” or the cholinergic anti-inflammatory pathway occurs when proinflammatory cytokines such as IL-1β and TNF-α stimulate the parasympathetic nervous system through receptors on the vagus nerve. Theafferent input travels to the nucleus solitarius and is relayed to the dorsal motor nucleus, resulting in an increase in acetylcholine release at cholinergic nerve terminals in the areas of inflammation. Activated macrophages have acetylcholine receptors that, when stimulated, decrease the release of proinflammatory cytokines (25,26). Beside the release of anti-inflammatory markers, this balance of the systems is crucial in limiting the overall stress response.

Moore et al. (15) also observed changes in the size of body fluid compartments, an effect which ends 4 to 5 days after injury with a shift to anabolism. The vasculature contracts, fluid is removed from the extracellular space and either moves back into cells or is excreted by the kidneys, and the intracellular shift is accompanied by an influx of protein and electrolytes. While the physiologic “signal” that initiates this transition is still unknown, it is telling that the transition occurs at the completion of the first wave of angiogenesis. The generation of a new vascular highway obviates the need for nutrient concentration gradients, increased vascular permeability, as well as water and electrolyte conservation; with the latter no longer a priority, a brisk diuresis results. In addition, as the intracellular space expands, increases in intracellular anions and cations are required. As these must come from the vascular space, resolution of catabolism is accompanied by decreases in serum levels of potassium, magnesium, and phosphate ions and, therefore, diuresis and decreases in serum electrolytes are the hallmarks of resolution of the stress response.
The cellular immune response to normal inflammatory stimuli involves neutrophils, monocytes (macrophages), lymphocytes, and APCs. Neutrophils are recruited to areas of injury early in the process by chemoattractant molecules (chemokines) such as CXCL2, CXCL8, CXCL16, VEGF, MIF, which are released by endothelial cells, macrophages (most importantly), and fibroblasts (27,28). Their function is repair and regeneration, more precisely removal of cellular debris by phagocytosis through secretion of lytic molecules such as digestive enzymes and free radicals. While the influx of neutrophils is self-limited, the rest of the response, which starts within hours of neutrophil influx, may be more persistent. It consists of infiltration by macrophages, APCs, and lymphocytes. Macrophages are of key importance in innate immunity, a process that is nonspecific and involves natural barriers such as skin, natural killer (NK) cells, and chemicals in the blood that act immediately upon antigen introduction. Macrophages respond to stimulation with phagocytosis of foreign or damaged material and secretion of cytokines that stimulate inflammation and also function as growth factors. In addition, macrophages contribute to adaptive immunity by presenting antigens, a function that also is served by APCs. Depending on the local environment, macrophages undergo specific differentiation into M1 and M2 phenotypes. The M1 polarization corresponds with the classically activated macrophage and has an acute proinflammatory phenotype, whereas the alternative M2 polarization antagonizes the inflammatory response and are involved in the regulation of immunity, tissue repair, and wound healing (29).

Antigen-presenting cells, such as dendritic cells, capture antigens and transport them to lymph nodes, where they are presented to T cells, initiating cell-mediated immunity. Follicular dendritic cells have a similar function except that they present antigens to B cells and therefore initiate humoral immunity. Lymphocytes are the prime components of the adaptive immune response and have specific receptors for antigens. B cells produce antibodies and are mediators of humoral immunity; T cells recognize antibodies and are mediators of cell-mediated immunity. T cells are further divided into CD4+ cells, which enhance or inhibit the immune response; CD8+ cells, which lyse other cells with intracellular pathogens; and NK cells, which do not express antigen receptors and contribute to innate immunity. Previous studies demonstrated that cytokines are centrally involved in regulation of adaptive immunity through control of T- and B-cell responses. The genetic deletion or immunoneutralization of specific cytokines was demonstrated to significantly reduce T-cell priming and memory responses, as well as cytokine production from T cells (30,31), and T-cell dependent antibody response. Activated T cells contribute to the auto/paracrine activation of IL-2, IL-2R, and IFN-γ production (32).

Adaptive immunity is antigen specific and can be divided into five phases. The first phase is presentation of the antigen to a B- or T cell by an APC. In the second phase, B- and T cells are activated, undergoing clonal expansion, differentiation, and antibody production. During the third or effector phase, antigens are eliminated. Decline is the fourth phase; the stimulus has been removed and there is apoptosis of immune cells and phagocytosis of cellular debris. This phase results in the surviving immune cells acquiring memory (33). As the process proceeds, there is a change in the phenotype of CD4+ T cells that is profoundly important. The early, protective phase of inflammation is characterized by an abundance of CD4+ T cells of the type 1 helper T-cell (T\textsubscript{H}1) phenotype. This results in secretion of proinflammatory cytokines such as IL-2, TNF-α, and interferon-γ. The switch to reconstitution is accompanied by a predominance of type 2 helper T cells (T\textsubscript{H}2), which secrete anti-inflammatory cytokines such as IL-4 and IL-10. In a normal stress response, immune function declines and the transition from T\textsubscript{H}1 to T\textsubscript{H}2 occurs by the fourth or fifth day; the switch from T\textsubscript{H}1 to T\textsubscript{H}2 may be hormonally mediated. It is known that cortisol and androgens, which are secreted in great quantities in catabolism, stimulate T\textsubscript{H}2 cell production. Figure 43.1 and Table 43.1 provide an overview of the various contributors to the host response mechanisms after injury.

**DIAGNOSIS**

The stress response is considered to be adaptive and vital in order that an injury might be survived. However, many aspects of the process may become excessive or unbalanced; this converts an adaptive response into a pathologic one. Risk factors that predispose to the development of an abnormal response include inadequate or delayed resuscitation, persistent inflammatory or infectious sources, baseline organ dysfunction, age older than 65 years, immunosuppression, alcohol abuse, malnutrition, and invasive instrumentation (34).

This abnormal and pathologic response was termed systemic inflammatory response syndrome (SIRS). If SIRS is suspected to be from an infectious cause, then the condition is referred to as sepsis or the sepsis syndrome. Initially, the normal stress response, SIRS, and sepsis may mimic each other and clinically, there is often a subtle transition from one to the other.

The definitions of SIRS, sepsis, and severe sepsis were phrased in 1992 and 2001 by the Sepsis Consensus Conference and revised in part by the Surviving Sepsis Campaign guidelines in 2012. There is an open debate about the gold standard in measuring organ dysfunction and malperfusion (35) and consensus is currently sought via task forces and Delphi procedures.

While sepsis will be discussed in detail in a later chapter (see Chapter 46), the concomitant state of immune incompetence requires further discussion. Historically, sepsis has been viewed as a condition ruled by uncontrolled inflammation. However, an increasing number of studies indicate that sepsis is in fact a state of inflammatory failure (36–39), resulting from a dysbalance between pro- and anti-inflammatory mechanisms. More specifically, sepsis is associated with an alteration in the adaptive immune response (40). The early phase of sepsis resembles normal stress, in that there is a hormonal milieu that stimulates T\textsubscript{H}2 responses and these responses are, indeed, observed; studies have shown that patients with sepsis have increased T\textsubscript{H}2 cells and IL-10 and that these levels predict mortality (41,42). However, as sepsis progresses, there is a profound endocrinopathy and progressive energy (18). That is, chronic critical illness is associated with a loss of T-cell responsiveness on all levels (43); this may reflect enhanced lymphocyte apoptosis (44–46). Hotchkiss et al. also demonstrated that there were decreased levels of follicular dendritic cells, B cells, and CD4+ T cells at the time of death of septic patients, resulting in impaired antigen presentation, antibody...
The ultimate result of immunosuppression is the development of sequential infections, often invoking the decision to withdraw therapy.

One major contributor to the development of complications from inflammation is the presence of comorbidities. Chronic comorbid conditions are present in over 50% of patients with sepsis and are associated with increased mortality (47–49). This is of particular relevance as the concerned patient population is getting older and presenting with an increasing number of comorbid conditions. Diseases reported to increase the risk of the normal stress response developing into sepsis are diabetes mellitus (DM), human immunodeficiency virus (HIV), chronic liver disease, and cancer (47). Esper et al. conducted a retrospective analysis that reviewed patients with the diagnosis of sepsis in U.S. acute care hospitals within a 25-year follow-up, characterizing the type and source of infections and comorbid diseases. They found that men were more likely than women, and African Americans were more likely than Caucasians, to develop sepsis. Non-Caucasian patients who were septic were more likely to have concomitant DM, HIV, chronic renal failure, and alcohol abuse; Caucasians had higher incidences of cancer and chronic obstructive pulmonary disease (COPD). The presence of one comorbidity increased the risk of developing at least one-organ-system failure by 30%. Those with two comorbidities had a 39% chance, and those with three or more had a 45% chance of developing acute organ failure (50).

It is not difficult to imagine how baseline insufficiencies affect the stress response. For example, the ability to maintain a circulatory system capable of providing oxygen and nutrients to areas of injury is paramount to survival; in the setting of infection, this challenge is exacerbated by the release of cytokines and other pro-inflammatory mediators that can disrupt normal physiological function.

### TABLE 43.1 Contributors to the Host Response to Injury

<table>
<thead>
<tr>
<th><strong>Cellular Contributors</strong></th>
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<tbody>
<tr>
<td>Organ-specific cells</td>
<td></td>
</tr>
<tr>
<td>- Cardiomyocytes</td>
<td></td>
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<tr>
<td>- Hepatocytes</td>
<td></td>
</tr>
<tr>
<td>- Others</td>
<td></td>
</tr>
<tr>
<td>Systemic cell types</td>
<td></td>
</tr>
<tr>
<td>- Adipose tissue</td>
<td></td>
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<tr>
<td>- Epithelial cells</td>
<td></td>
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<tr>
<td>- Endothelial cells</td>
<td></td>
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<tr>
<td>- Fibroblasts</td>
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<table>
<thead>
<tr>
<th><strong>Blood-Derived Contributors</strong></th>
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<tbody>
<tr>
<td>Blood originated cells</td>
<td></td>
</tr>
<tr>
<td>- Neutrophils</td>
<td></td>
</tr>
<tr>
<td>- Macrophages/monocytes (M1, M2)</td>
<td></td>
</tr>
<tr>
<td>- Dendritic cells</td>
<td></td>
</tr>
<tr>
<td>- B cells, T cells (α1, α2), natural killer cells</td>
<td></td>
</tr>
<tr>
<td>- Thrombocytes</td>
<td></td>
</tr>
<tr>
<td>Complement system</td>
<td></td>
</tr>
<tr>
<td>- C3a, C5a, C5aR, C5b</td>
<td></td>
</tr>
<tr>
<td>Coagulation system</td>
<td></td>
</tr>
<tr>
<td>- Prothrombin, protein C</td>
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<table>
<thead>
<tr>
<th><strong>Chemokines/Cytokines</strong></th>
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<tbody>
<tr>
<td>Proinflammatory</td>
<td></td>
</tr>
<tr>
<td>- Inflammasome (NLPR3/ASC/caspase-1)</td>
<td></td>
</tr>
<tr>
<td>- CXCL12, CXCL8, CXCL16, - IL-1β, IL-2, IL-6, IL-18, IFN-γ</td>
<td></td>
</tr>
<tr>
<td>- VEGF, MIF, TNF-α</td>
<td></td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td></td>
</tr>
<tr>
<td>- IL-4, IL-10, IL-1RA</td>
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</table>

*This list is by no means exhaustive but mentions, subjectively, the most important effectors in accordance with the chapter’s text.*
of underlying coronary artery disease (CAD), this ability may be impaired. Kern et al. (51) found that patients with CAD have significantly decreased cardiac index and oxygen delivery and, not surprisingly, an increased oxygen extraction ratio during sepsis. They also showed that these patients had increased endothelial adhesion molecule expression, which may correlate with the severity of sepsis, shock, and organ failure and predict poor outcome (52,53). Chronic pulmonary disease, regardless of the etiology, increases the chance of intubation and the requirement for prolonged ventilatory support. Intubation places the patient at risk for ventilator-associated pneumonia, aspiration, and respiratory muscle atrophy, and is associated with a prolonged, cost-intensive, treatment. A patient with chronic renal or liver failure is at risk for anemia, coagulopathy, and immunosuppression prior to being injured. With an impaired functional reserve in vital organs and responses, the stress response to injury has a high likelihood of progressing to a state of prolonged critical illness.

Beside these baseline characteristics, several relevant polymorphisms have been uncovered during the last decade, which are of importance for the development of innate immunity and susceptibility against associated complications (54). For example, the genotype of the proinflammatory cytokine TNF-α or MIF has been shown to affect susceptibility or clinical severity of different inflammatory or infectious diseases (55). In a large cohort of patients with pneumonia and at risk to develop septic shock, Yende et al. demonstrated that a high MIF expression genotype was associated with a significantly reduced mortality. These findings were unexpected, since an overwhelming inflammatory response was supposed to represent the most harmful stimulus within the pathophysiology of sepsis. Likewise, Calandra et al. reported the crucial role of MIF in macrophagic bactericidal properties. MIF-deficient macrophages exhibited an impaired killing of gram-negative bacteria that could be restored by an addition of recombinant MIF (56).

TREATMENT

Multiple clinical trials failed to show protective treatment-improved outcome in septic patients. The vast majority of trials focused on blocking the initial hyperinflammatory, cytokine-mediated phase of the disorder. Based on results from experimental studies where inhibition of TNF-α or IL-1β with neutralizing antibodies, soluble receptors, or receptor antagonists protected animals from the deleterious effects of high-grade bacteremia and endotoxemia, clinical trials aimed to confirm these findings in septic patients (57,58). Surprisingly, all studies failed to show any beneficial effects of pharmacologic antagonization of inflammatory mediators in sepsis (59). The underlying reasons remain speculative, but include the choice of heterogeneous patient cohorts. Furthermore, it is tempting to speculate that previous treatments were applied too late, when circulating levels of TNF-α and IL-1β had already returned to baseline values.

The last decade was shaped by substantial improvements in the treatment protocols emphasizing the necessity of early timing of treatment bundles, wherein anti-infectious therapies and restoration of adequate tissue perfusion were of particular relevance. Today, the majority of patients survive the initial hyperinflammatory phase, but are still exposed to severe complications during the protracted immunosuppressive phase (60).

Deaths during this immunosuppressive phase result typically from failure to control the primary infection or the acquisition of secondary hospital-acquired infections (61). Therefore many attempts are under investigation, focusing on anticytokine and immunomodulatory therapies during this relevant period (61); additionally, emerging phase II clinical trials of immunotherapies have brought cautious optimism to the field, but need to be confirmed in large-scale multicenter trials (62–66). Further, there have been several experiments conducted with mice in septic or hemorrhagic shock showing increased mortality from immunosuppression after β-blockade (67,68). Adequate analgesia via epidural and intravenous use of agents such as opiates, α-blockers, and local anesthetics have been shown to both decrease inflammation and improve immune function (69–72).

Considering the prevention of both postoperative infection and excessive inflammation in cardiac surgery patients, recent evidence on corticosteroids provides conflicting evidence that attenuating the inflammatory response may result in clinical benefit. The dexamethasone for cardiac surgery trial randomized high-risk cardiac surgery patients to a single intraoperative dose of dexamethasone or placebo, but failed to demonstrate a benefit in treated patients (73). In the same vein, the Steroids In CaRdiac Surgery (SiRS) Trial did not provide support for this hypothesis, stating that perioperative administration of pulse dose methylprednisolone did not reduce the risk of death at 30 days (74).

Trials of both medical devices and immune biologics aiming to eliminate the excessive inflammatory response are ongoing. Early results suggest complement inhibition to be a promising adjunctive therapy in infectious as well as noninfectious inflammatory disorders (75).

CONTROVERSIES

Given the multitude of failed clinical trials in septic patients, a better understanding of different immunologic phases seems mandatory to optimize the ongoing strategies of immune response modulation.

Recent experiences of failed studies on anti–toll-like receptor 4 (TLR-4), recombinant activated protein C, and anti–TNF-α therapies indicate that a higher precision is needed when trying to influence inflammatory pathophysiology (62–66). Furthermore, recent findings of a large clinical trial targeting oxidative stress in critically ill patients demonstrated no clinical benefit of antioxidant therapy and a trend toward increased mortality with glutamine administration (76). The reasons for the disappointing results are speculative; beside the question of dose and timing, adverse off-target effects may have contributed to their failure. Pertinent to possible off-target effects, it is important to remember that ROS are critical signaling molecules for cell homeostasis and adaptation to stress (e.g., hypoxia), processes that may be impaired with antioxidants. In addition, it has been recognized that ROS are critical signaling molecules essential for optimal function of innate and adaptive immunity. Both types of immunity are required to fight infection, a frequent contributor to morbidity and mortality in critically ill patients.

As many early-phase inflammatory cytokines operate concurrently and redundantly, identifying and targeting upstream triggers may generate therapies with broad downstream effects—yet not necessarily benefits. In the same way high
precision surgery requires paramount knowledge of anatomy, immunomodulatory pharmacotherapy requires the same precision regarding signaling cascades and a detailed knowledge of consequences we are, perhaps, still lacking.

**Key Points**

- Injury is present in the form of elective surgery, trauma, infection, and other illnesses.
- The host response to injury is janiform. While harmful if exaggerated, it is mandatory to induce regeneration and preservation strategies.
- Balance is the hallmark of a physiologic host response. Pre-existing disease and persistent hypermetabolism offset this balance and pathologic conditions prevail.
- Both anti-inflammatory and proinflammatory strategies may offer therapeutic benefit restoring balance, yet so far most modulating therapies disappointed.

**ACKNOWLEDGMENTS**

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