

## REVIEW ARTICLE

## MEDICAL PROGRESS

## The Pathophysiology and Treatment of Sepsis

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**S**EPSIS IS THE LEADING CAUSE OF DEATH IN CRITICALLY ILL PATIENTS IN the United States. Sepsis develops in 750,000 people annually, and more than 210,000 of them die.<sup>1,2</sup> After numerous unsuccessful trials of antiinflammatory agents in patients with sepsis, investigators doubted that mortality could be decreased. Advances in unraveling the pathophysiology and genetic basis for the host response to sepsis have changed the prevailing understanding of the syndrome, and several therapies have demonstrated surprising efficacy. In this article, we examine evolving concepts of sepsis and discuss new and potential therapies.

## A DISORDER DUE TO UNCONTROLLED INFLAMMATION?

The prevailing theory has been that sepsis represents an uncontrolled inflammatory response.<sup>3-5</sup> Lewis Thomas popularized this notion when he wrote that “the microorganisms that seem to have it in for us . . . turn out . . . to be rather more like bystanders. . . . It is our response to their presence that makes the disease. Our arsenals for fighting off bacteria are so powerful . . . that we are more in danger from them than the invaders.”<sup>6</sup> A consensus conference defined sepsis as “the systemic inflammatory response syndrome that occurs during infection.”<sup>3</sup> Numerous trials were conducted of agents that block the inflammatory cascade — corticosteroids,<sup>7</sup> antientotoxin antibodies,<sup>8</sup> tumor necrosis factor (TNF) antagonists,<sup>9,10</sup> interleukin-1-receptor antagonists,<sup>11</sup> and other agents.<sup>12</sup> The failure of antiinflammatory agents led investigators to question whether death in patients with sepsis results from uncontrolled inflammation.<sup>4,13-15</sup> Clinical trials of treatments for sepsis are difficult because of the heterogeneity of patients and the high rates of culture-negative sepsis. Interpretation is complicated, because the analysis of outcomes generates post hoc stratifications that have not been prospectively defined.

The theory that death from sepsis was attributable to an overstimulated immune system was based on studies in animals that do not seem to reflect the clinical picture in humans.<sup>16-18</sup> These studies used large doses of endotoxin or bacteria; consequently, levels of circulating cytokines such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) were exponentially higher in animals than they are in patients with sepsis.<sup>17</sup> In these studies, the animals died from “cytokine storm,” and compounds and macromolecules that block these mediators improved survival.<sup>16-18</sup>

In certain forms of sepsis — for example, meningococemia — circulating TNF- $\alpha$  levels are high and correlate with mortality.<sup>19,20</sup> Of 55 children with severe infectious purpura (32 of them with *Neisseria meningitidis* infection), 91 percent had elevated levels of circulating TNF- $\alpha$ .<sup>19</sup> Nevertheless, studies have shown that the frequency of an exaggerated systemic inflammatory response is lower than it was originally thought to be.<sup>21-24</sup> Debets et al. reported that only 11 of 43 patients with sepsis had detectable circulating TNF (limit of detection, 5 to 10 pg per milliliter).<sup>21</sup> In another study of 87 pa-

tients with sepsis, fewer than 10 percent had measurable TNF- $\alpha$  or interleukin-1 $\beta$ .<sup>22,23</sup>

Although cytokines are considered to be culprits, they also have beneficial effects in sepsis. Studies in an animal model of peritonitis demonstrated that blocking TNF- $\alpha$  worsens survival.<sup>25,26</sup> Combination immunotherapy against TNF- $\alpha$  and interleukin-1 receptors was fatal in a neutropenic model of sepsis.<sup>27</sup> In clinical trials, a TNF antagonist increased mortality.<sup>9</sup> The role of TNF- $\alpha$  in combating infection has recently been underscored by the finding that sepsis and other infectious complications developed in patients with rheumatoid arthritis who were treated with TNF antagonists.<sup>28</sup>

The debate about the merits of inhibiting cytokines in patients with sepsis has been rekindled by a recent trial that indicated that a subgroup of patients with sepsis who had therapy directed against TNF- $\alpha$  had improved survival.<sup>29</sup> Also, a meta-analysis of clinical trials of antiinflammatory agents in patients with sepsis showed that although high doses of antiinflammatory agents were generally harmful in such patients, a subgroup of patients (approximately 10 percent) benefited.<sup>13</sup>

Advances in our understanding of cell-signaling pathways that mediate the response to microbes have demonstrated that the concept of blocking endotoxin in order to prevent septic complications may be simplistic. Cells of the innate immune system recognize microorganisms and initiate responses through pattern-recognition receptors called toll-like receptors (TLRs).<sup>30-32</sup> Insight into the role of TLRs in combating infection has been provided by studies in C3H/HeJ mice,<sup>30</sup> which are resistant to endotoxin because of a mutation in the toll-like receptor 4 gene (TLR4). Despite their resistance to endotoxin, these mice have increased mortality with authentic sepsis.<sup>33,34</sup> TLR4 mutations have been identified in humans and may make persons more susceptible to infection.<sup>35</sup> Therefore, although endotoxin has deleterious effects, total blockade of endotoxin may be detrimental. Reasons for the failure of monoclonal antiendotoxin antibodies to improve outcomes in trials involving patients with sepsis are complex.<sup>36</sup>

#### FAILURE OF THE IMMUNE SYSTEM?

Patients with sepsis have features consistent with immunosuppression, including a loss of delayed hypersensitivity, an inability to clear infection, and

a predisposition to nosocomial infections.<sup>37-39</sup> One reason for the failure of antiinflammatory strategies in patients with sepsis may be a change in the syndrome over time. Initially, sepsis may be characterized by increases in inflammatory mediators; but as sepsis persists, there is a shift toward an antiinflammatory immunosuppressive state.<sup>38,39</sup> There is evidence of immunosuppression in sepsis from studies showing that lipopolysaccharide-stimulated whole blood from patients with sepsis releases markedly smaller quantities of the inflammatory cytokines TNF- $\alpha$  and interleukin-1 $\beta$  than does that of control patients.<sup>40</sup> The adverse sequelae of sepsis-induced immunosuppression were reversed with the administration of interferon- $\gamma$  in patients with sepsis.<sup>41</sup> This immune stimulant restored macrophage TNF- $\alpha$  production and improved survival.<sup>41</sup>

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#### MECHANISMS OF IMMUNE SUPPRESSION IN SEPSIS

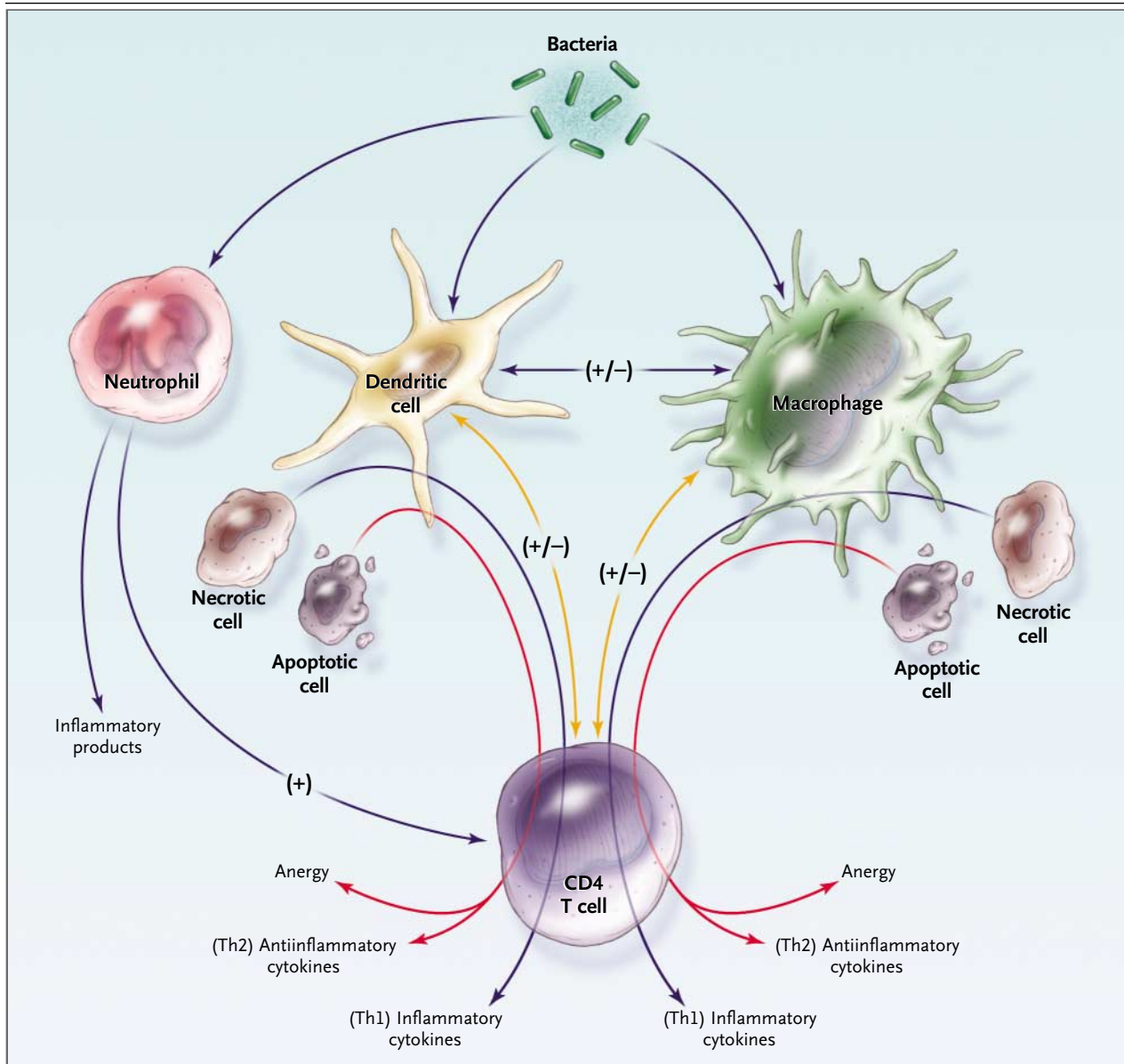
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##### A SHIFT TO ANTIINFLAMMATORY CYTOKINES

Activated CD4 T cells are programmed to secrete cytokines with either of two distinct and antagonistic profiles.<sup>42,43</sup> They secrete either cytokines with inflammatory (type 1 helper T-cell [Th1]) properties, including TNF- $\alpha$ , interferon- $\gamma$ , and interleukin-2, or cytokines with antiinflammatory (type 2 helper T-cell [Th2]) properties — for example, interleukin-4 and interleukin-10 (Fig. 1). The factors that determine whether CD4 T cells have Th1 or Th2 responses are unknown but may be influenced by the type of pathogen, the size of the bacterial inoculum, and the site of infection.<sup>42</sup> Mononuclear cells from patients with burns or trauma have reduced levels of Th1 cytokines but increased levels of the Th2 cytokines interleukin-4 and interleukin-10, and reversal of the Th2 response improves survival among patients with sepsis.<sup>38,44</sup> Other studies have demonstrated that the level of interleukin-10 is increased in patients with sepsis and that this level predicts mortality.<sup>43,45</sup>

##### ANERGY

Anergy is a state of nonresponsiveness to antigen. T cells are anergic when they fail to proliferate or secrete cytokines in response to their specific antigens. Heidecke et al. examined T-cell function in patients with peritonitis and found that they had decreased Th1 function without increased Th2 cytokine production, which is consistent with anergy.<sup>46</sup> Defective T-cell proliferation and cytokine secretion



**Figure 1.** The Response to Pathogens, Involving “Cross-Talk” among Many Immune Cells, Including Macrophages, Dendritic Cells, and CD4 T Cells.

Macrophages and dendritic cells are activated by the ingestion of bacteria and by stimulation through cytokines (e.g., interferon- $\gamma$ ) secreted by CD4 T cells. Alternatively, CD4 T cells that have an antiinflammatory profile (type 2 helper T cells [Th2]) secrete interleukin-10, which suppresses macrophage activation. CD4 T cells become activated by stimulation through macrophages or dendritic cells. For example, macrophages and dendritic cells secrete interleukin-12, which activates CD4 T cells to secrete inflammatory (type 1 helper T-cell [Th1]) cytokines. Depending on numerous factors (e.g., the type of organism and the site of infection), macrophages and dendritic cells will respond by inducing either inflammatory or antiinflammatory cytokines or causing a global reduction in cytokine production (anergy). Macrophages or dendritic cells that have previously ingested necrotic cells will induce an inflammatory cytokine profile (Th1). Ingestion of apoptotic cells can induce either an anti-inflammatory cytokine profile or anergy. A plus sign indicates up-regulation, and a minus sign indicates down-regulation; in cases where both a plus sign and a minus sign appear, either up-regulation or down-regulation may occur, depending on a variety of factors.

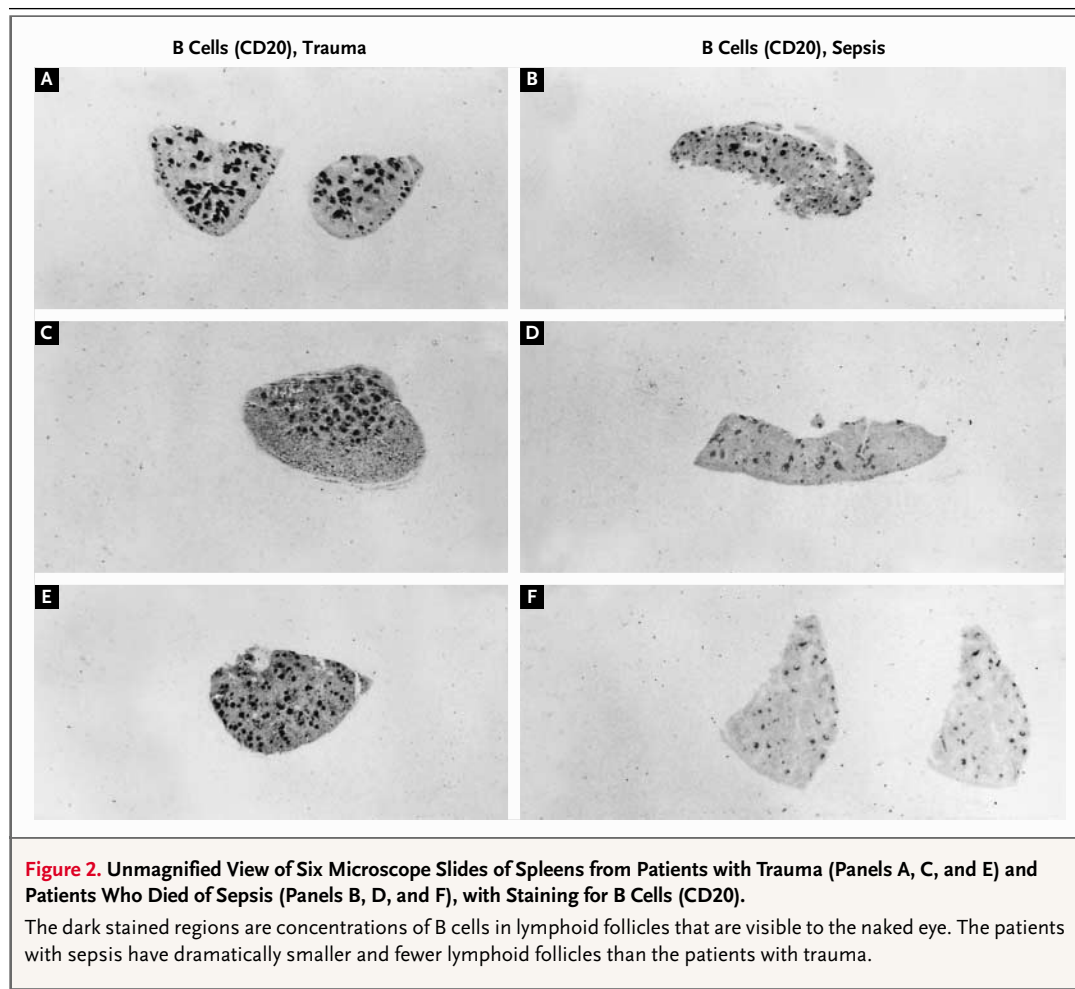
correlated with mortality.<sup>46</sup> Patients with trauma or burns have reduced levels of circulating T cells, and their surviving T cells are anergic.<sup>47</sup>

Apoptotic cell death may trigger sepsis-induced anergy. Although the conventional belief was that cells die by necrosis, recent work has shown that cells can die by apoptosis — genetically programmed cell death. In apoptosis, cells “commit suicide” by the activation of proteases that disassemble the cell.<sup>48,49</sup> Large numbers of lymphocytes and gastrointestinal epithelial cells die by apoptosis during sepsis.<sup>50-52</sup> A potential mechanism of lymphocyte apoptosis may be stress-induced endogenous release of glucocorticoids.<sup>53,54</sup> The type of cell death determines the immunologic function of surviving immune cells (Fig. 1).<sup>55-57</sup> Apoptotic cells induce anergy or antiinflammatory cytokines that impair the response to pathogens, whereas necrotic cells cause immune stimulation and enhance antimicrobial defenses (Fig. 1).<sup>55-57</sup>

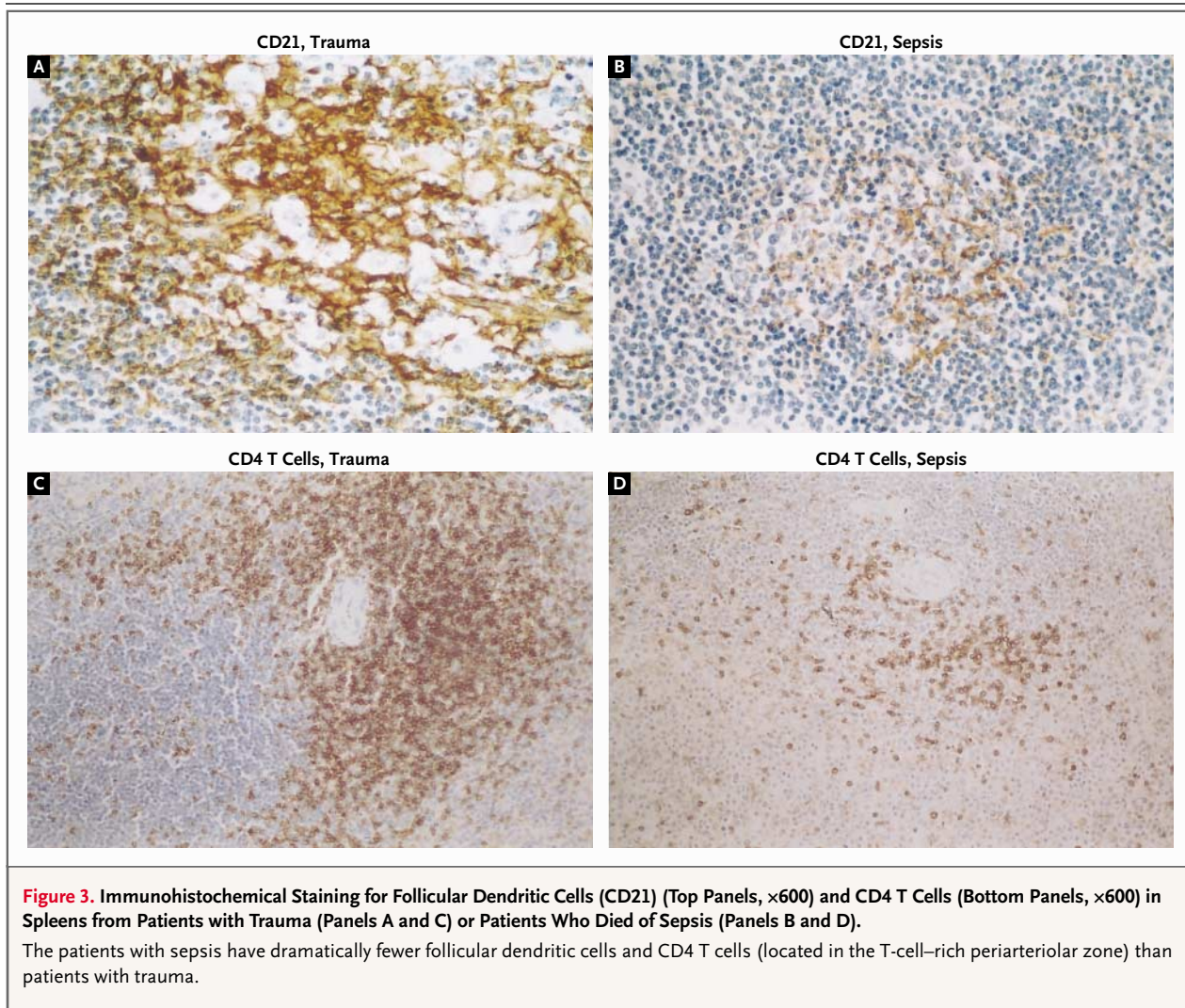
#### DEATH OF IMMUNE CELLS

Autopsy studies in persons who had died of sepsis disclosed a profound, progressive, apoptosis-induced loss of cells of the adaptive immune system.<sup>50-52</sup> Although no loss of CD8 T cells, natural killer cells, or macrophages occurred, sepsis markedly decreased the levels of B cells (Fig. 2), CD4 T cells (Fig. 3), and follicular dendritic cells (Fig. 3). The loss of lymphocytes and dendritic cells was especially important, because it occurred during life-threatening infection, when clonal expansion of lymphocytes might have been expected.

The magnitude of the apoptosis-induced loss in lymphocytes during sepsis was apparent in examinations of the circulating lymphocyte count in patients.<sup>50</sup> In one study, 15 of 19 patients with sepsis had absolute lymphocyte counts below the lower limit of normal (a mean [ $\pm$ SD] of  $500 \pm 270$  per cubic millimeter vs. the lower limit of 1200 per cubic millimeter). Losses of B cells, CD4 T cells, and dendrit-







ic cells decrease antibody production, macrophage activation, and antigen presentation, respectively. The potential importance of the depletion of lymphocytes is illustrated by studies in animals showing that prevention of lymphocyte apoptosis improves the likelihood of survival.<sup>58-61</sup> Immune defects identified in patients with sepsis, including monocyte dysfunction,<sup>41,62,63</sup> are listed in Table 1.

#### REAPPRAISAL OF LEWIS THOMAS'S THEORY

Investigators are challenging Lewis Thomas's theory<sup>6</sup> that the body's primary response to infec-

tion and injury is uncontrolled hyperinflammation.<sup>4,13,14,64</sup> Munford and Pugin maintain that the body's normal stress response is activation of anti-inflammatory mechanisms and that, outside of affected tissues, the body's systemic antiinflammatory responses predominate.<sup>64</sup> They postulate that immune cells and cytokines have both pathogenic and protective roles and that blocking these mediators may worsen the outcome.<sup>64</sup> Heidecke et al. examined T-cell function in patients with sepsis and reported that immunosuppression was evident at the onset of sepsis, suggesting a primary hypimmune response.<sup>46</sup>

Weighardt and associates examined lipopoly-

**Table 1. Potential Mechanisms of Immune Suppression in Patients with Sepsis.\***

Shift from an inflammatory (Th1) to an antiinflammatory (Th2) response
Anergy
Apoptosis-induced loss of CD4 T cells, B cells, and dendritic cells
Loss of macrophage expression of major-histocompatibility-complex class II and costimulatory molecules
Immunosuppressive effect of apoptotic cells

\* Th1 denotes type 1 helper T cell, and Th2 type 2 helper T cell.

saccharide-stimulated production of cytokines by monocytes in patients with sepsis that occurred after major visceral surgery.<sup>65</sup> Postoperative sepsis was associated with the immediate onset of defects in the production of both inflammatory and antiinflammatory cytokines by monocytes, and survival among patients with sepsis correlated with the recovery of the inflammatory but not the antiinflammatory response.<sup>65</sup> These investigators concluded that immunosuppression was a primary rather than a compensatory response to sepsis.<sup>65</sup> Others postulate a sequential response to sepsis, with initial marked inflammation followed by immunosuppression.<sup>14,38,39</sup>

#### HOST GENETIC FACTORS

On the basis of studies in identical twins and adoptees, genetic factors are known to be major determinants of susceptibility to death from infectious disease.<sup>66</sup> Some persons have single base-pair alterations (single-nucleotide polymorphisms) in genes controlling the host response to microbes.<sup>67-69</sup> Identified alterations include polymorphisms in TNF receptors, interleukin-1 receptors, Fcγ receptors, and TLRs.<sup>67-69</sup> Polymorphisms in cytokine genes may determine the concentrations of inflammatory and antiinflammatory cytokines produced and may influence whether persons have marked hyperinflammatory or hypoinflammatory responses to infection. The risk of death among patients with sepsis has been linked to genetic polymorphisms for TNF-α and TNF-β.<sup>69</sup> Trials examining the effect of polymorphisms in patients with pneumonia and sepsis are under way; such polymorphisms may ultimately be used to identify patients

at high risk for the development of sepsis and organ dysfunction during infection. Thus, physicians may, in the future, be able to use genetic information to dictate immune-based therapy to modulate the response in a given patient.

#### SURPRISING INSIGHTS ABOUT NEUTROPHILS

Neutrophils have been regarded as double-edged swords in sepsis. Although neutrophils were thought to be essential for the eradication of pathogens, excessive release of oxidants and proteases by neutrophils was also believed to be responsible for injury to organs. Because of the intrapulmonary sequestration of neutrophils and the frequent complication of the acute respiratory distress syndrome in patients with sepsis, this link between overly exuberant neutrophil activation and organ injury was thought to affect the lungs in particular.<sup>70</sup> Although findings from studies in animals implicated neutrophil-mediated injury, other studies in which granulocyte colony-stimulating factor (G-CSF) was used — to increase the number of neutrophils and enhance their function — demonstrated improved survival among patients with sepsis.

Two randomized trials of G-CSF were conducted in patients with community-acquired and hospital-acquired pneumonia.<sup>71,72</sup> Despite an increase in the white-cell count to 70,000 per cubic millimeter, there was no evidence of adverse effects on lung function in patients with community-acquired pneumonia.<sup>71</sup> Although a subgroup of patients with multilobar pneumonia had fewer complications and shorter stays in the intensive care unit with G-CSF, there was no improvement in survival. Similarly, hospitalized patients with community-acquired or nosocomial pneumonia who were treated with G-CSF had no survival benefit, no decrease in organ dysfunction, and no decrease in the number of days in intensive care.<sup>72</sup>

Although marked leukocytosis resulting from G-CSF was not injurious, it is not necessarily possible to extrapolate from such data whether marked leukocytosis would be harmful in patients with severe sepsis. However, these two clinical studies imply that blocking neutrophil function to prevent complications of sepsis would be unlikely to be beneficial. Furthermore, therapies aimed at enhancing the number or function of neutrophils in patients with sepsis are also unlikely to be efficacious.

## LESSONS FROM AUTOPSY STUDIES

Autopsy studies in persons who died in the intensive care unit show that the failure to diagnose and appropriately treat infections with antibiotics or surgical drainage is the most common avoidable error.<sup>73,74</sup> Our laboratory conducted an autopsy study of 20 patients who died in intensive care units<sup>50</sup>; consent was obtained immediately after each patient's death, so that tissues were usually acquired within 30 to 90 minutes after death, thereby permitting tissue morphology to be assessed before autolytic changes occurred. Autopsies were also performed in a control group consisting of patients who had died while critically ill but who did not have clinical sepsis. Immunohistochemical analysis showed that in the majority of patients with sepsis, only two types of cells — lymphocytes and gastrointestinal epithelial cells — were dying; this finding parallels those of studies in animals.<sup>39,54,75</sup> As had been noted previously, there was a profound loss of cells of the adaptive immune system. Lymphocytes and gastrointestinal epithelial cells normally undergo rapid turnover through apoptosis, and sepsis most likely accelerates these physiologic processes. Focal necrosis occurred in hepatocytes in the region of the central vein (presumably because this region is vulnerable to hypoxia) in 7 of 20 patients, as well as in the brain and heart in 3 patients who had evidence of infarction before death.

CELLULAR HIBERNATION  
AS A MECHANISM  
OF ORGAN DYSFUNCTION

Another intriguing finding from the autopsy study was a discordance between histologic findings and the degree of organ dysfunction seen in patients who died of sepsis.<sup>50</sup> Cell death in the heart, kidney, liver, and lung was relatively minor and did not reflect the clinical evidence of more profound organ dysfunction. There was no evidence of injury to cardiac myocytes in patients with sepsis who had myocardial depression. (No patient had meningococcemia, which causes myocarditis with infiltration of organisms and granulocytes.) Histologic findings in patients with sepsis and acute renal failure showed only focal injury with preservation of normal glomeruli and renal tubules.<sup>50</sup> These results are similar to those of studies in patients with acute renal failure in which microscopy showed a dissociation between the degree of tubular necro-

sis and the level of renal dysfunction.<sup>76,77</sup> Most patients who survive sepsis and acute renal failure recover base-line renal function, suggesting that renal-cell death is not overwhelming during sepsis.<sup>78</sup>

We speculate that much organ dysfunction in patients with sepsis can be explained by "cell hibernation" or "cell stunning," as occurs during myocardial ischemia.<sup>79</sup> Presumably, sepsis activates defense mechanisms that cause cellular processes to be reduced to basic "housekeeping" roles. A possible molecular basis for cellular stunning was suggested by work from the laboratory of Fink et al.,<sup>80</sup> who showed that immunostimulated enterocytes have diminished oxygen consumption as a result of depletion of nicotinamide adenine dinucleotide secondary to activation of the nuclear enzyme polyadenosine diphosphate (ADP)-ribose polymerase by peroxynitrite or other oxidants.

## DEATH OF PATIENTS WITH SEPSIS

No autopsy studies have revealed why patients with sepsis die. Occasionally, a patient with sepsis may die of refractory shock, but this is exceptional. Although patients with sepsis have profound myocardial depression, cardiac output is usually maintained because of cardiac dilatation and tachycardia.<sup>81</sup> Although the acute respiratory distress syndrome frequently develops in patients with sepsis, such patients rarely die of hypoxemia or hypercarbia.<sup>82</sup> Renal failure is common, but that alone is not fatal, because dialysis may be used. Liver dysfunction rarely progresses to hepatic encephalopathy. Thus, the exact cause of death in patients with sepsis remains elusive. Many patients die when care is withdrawn or not escalated when families, in consultation with physicians, decide that continued therapy is futile.

NEW CONCEPTS IN THE  
TREATMENT OF SEPSIS

Physicians caring for patients in intensive care units need a thorough knowledge of common infectious and noninfectious causes of fever in this population of patients (Table 2). Many patients in whom sepsis develops — for example, elderly patients or patients with uremia — do not become febrile.<sup>83</sup> The lack of an apparent acute-phase response in patients with sepsis is associated with high mortality and may reflect the immunosuppressive phase of sepsis. Early manifestations of sepsis include sub-



**Table 2. Infectious and Noninfectious Causes of Fever in the Intensive Care Unit.**

Infected intravascular catheters
Sinusitis or otitis media (in patients with intranasal devices such as nasogastric tubes or nasal endotracheal tubes)
Acalculous cholecystitis
Drug fever
Pulmonary emboli
Deep venous thrombosis
Central fever (in patients with head trauma)
<i>Clostridium difficile</i> colitis
Postcardiotomy syndrome
Secondary infection by resistant organisms
Fungal infection

tle changes in mental status, minor increases or decreases in white-cell count or neutrophil percentage, or elevated blood glucose levels. Early recognition of sepsis is a key to successful treatment.

#### ACTIVATED PROTEIN C

Recombinant human activated protein C, an anticoagulant, is the first antiinflammatory agent that has proved effective in the treatment of sepsis.<sup>84,85</sup> In patients with sepsis, the administration of activated protein C resulted in a 19.4 percent reduction in the relative risk of death and an absolute risk reduction of 6.1 percent.<sup>84</sup> Activated protein C inactivates factors Va and VIIIa, thereby preventing the generation of thrombin.<sup>85</sup> The efficacy of an anticoagulant agent in patients with sepsis has been attributed to feedback between the coagulation system and the inflammatory cascade.<sup>85</sup> Inhibition of thrombin generation by activated protein C decreases inflammation by inhibiting platelet activation, neutrophil recruitment, and mast-cell degranulation. Activated protein C has direct antiinflammatory properties, including blocking of the production of cytokines by monocytes and blocking cell adhesion.

A puzzling issue is why activated protein C was successful whereas two other anticoagulants — antithrombin III<sup>86</sup> and tissue factor–pathway inhibitor — failed as treatments of sepsis. A possible explanation for the failure of these two anticoagulant agents is that they work at different sites in the coagulation cascade. Also, activated protein C has

antiapoptotic actions that may contribute to its efficacy.<sup>87</sup>

The debate regarding the appropriate use of activated protein C, as well as its potential adverse effects, particularly bleeding, has been discussed in recent articles.<sup>88-90</sup> A major risk associated with activated protein C is hemorrhage; in a study of activated protein C, 3.5 percent of patients had serious bleeding (intracranial hemorrhage, a life-threatening bleeding episode, or a requirement for 3 or more units of blood), as compared with 2 percent of patients who received placebo ( $P < 0.06$ ). With open-label use of activated protein C after the trial, 13 of 520 patients (2.5 percent) had intracranial hemorrhage.<sup>88</sup> Caution is advised in the use of activated protein C in patients with an international normalized ratio greater than 3.0 or a platelet count of less than 30,000 per cubic millimeter. Currently, activated protein C is approved only for use in patients with sepsis who have the most severe organ compromise and the highest likelihood of death. Use of activated protein C is restricted in many hospitals to the more seriously ill patients who meet the criteria for sepsis specified by the Acute Physiology and Chronic Health Evaluation (APACHE II) scoring system.

#### INTENSIVE INSULIN THERAPY FOR HYPERGLYCEMIA

Van den Berghe et al. demonstrated that intensive insulin therapy that maintained the blood glucose level at 80 to 110 mg per deciliter (4.4 to 6.1 mmol per liter) resulted in lower morbidity and mortality among critically ill patients than did conventional therapy that maintained the blood glucose level at 180 to 200 mg per deciliter (10.0 to 11.1 mmol per liter).<sup>91</sup> Intensive insulin therapy reduced the frequency of episodes of sepsis by 46 percent. Patients with bacteremia who were treated with intensive insulin therapy had lower mortality than those who received conventional therapy (12.5 percent vs. 29.5 percent). Insulin therapy reduced the rate of death from multiple-organ failure among patients with sepsis, regardless of whether they had a history of diabetes.

The protective mechanism of insulin in sepsis is unknown. The phagocytic function of neutrophils is impaired in patients with hyperglycemia, and correcting hyperglycemia may improve bacterial phagocytosis. Another potential mechanism involves the antiapoptotic effect of insulin.<sup>92</sup> Insulin prevents apoptotic cell death from numerous stimu-



li by activating the phosphatidylinositol 3-kinase–Akt pathway.<sup>90</sup> Regardless of mechanism, it seems reasonable to control blood glucose more tightly in critically ill patients. Clinicians must avert hypoglycemic brain injury in attempting to maintain the blood glucose level at 80 to 110 mg per deciliter. Frequent monitoring of blood glucose is imperative, and studies are needed to determine whether less tight control of blood glucose — for example, a blood glucose level of 120 to 160 mg per deciliter (6.7 to 8.9 mmol per liter) — provides similar benefits.

#### VOLUME RESUSCITATION

Another recent study by Rivers et al. showed that early aggressive therapy that optimized cardiac preload, afterload, and contractility in patients with severe sepsis and septic shock improved the likelihood of survival.<sup>93</sup> Rivers et al. used infusions of colloid or crystalloid, vasoactive agents, and transfusions of red cells to increase oxygen delivery. Resuscitation end points chosen for assessment of the adequacy of oxygen delivery were the normalization of values for mixed venous oxygen saturation, lactate concentration, base deficit, and pH. Patients in the group that received early goal-directed therapy received more fluid, inotropic support, and blood transfusions during the first six hours than did control patients, who received standard resuscitation therapy. During the interval from 7 to 72 hours, patients in the group receiving early goal-directed treatment had a higher mean central venous oxygen concentration, a lower mean lactate concentration, a lower mean base deficit, and a higher mean pH than the control group. Mortality was 30.5 percent in the group receiving early goal-directed treatment, as compared with 46.5 percent in the control group ( $P=0.009$ ). Thus, early therapeutic intervention to restore balance between oxygen delivery and oxygen demand improved survival among patients presenting with severe sepsis. The use of objective measures, including lactate concentration, base deficit, pH, and possibly central venous oxygen saturation, in the follow-up of patients who are receiving resuscitation therapy is advisable.

#### CORTICOSTEROIDS

Administration of high doses of corticosteroids (e.g., 30 mg of methylprednisolone per kilogram of body weight) does not improve survival among

patients with sepsis and may worsen outcomes by increasing the frequency of secondary infections.<sup>94</sup> Despite the negative effects of high-dose corticosteroids, a 2001 study by Annane indicated that patients with sepsis who are extremely ill and have persistent shock requiring vasopressors and prolonged mechanical ventilation may benefit from “physiologic” doses of corticosteroids.<sup>95</sup> It is postulated that such patients may have “relative” adrenal insufficiency despite elevated levels of circulating cortisol.<sup>96</sup>

The proposed explanation for the physiological response to corticosteroids (despite normal or elevated plasma cortisol levels) is desensitization of corticosteroid responsiveness with down-regulation of adrenergic receptors.<sup>96</sup> Catecholamines increase arterial pressure through effects on adrenergic receptors of the vasculature; corticosteroids increase the expression of adrenergic receptors. Testing involving stimulation by adrenocorticotrophic hormones may not be useful in identifying patients with relative adrenal insufficiency. Such patients may have markedly elevated base-line plasma cortisol levels and a blunted response to stimulation by adrenocorticotrophic hormones. A random plasma cortisol concentration of less than 20  $\mu\text{g}$  per deciliter suggests an inadequate adrenal response to stress.<sup>96</sup>

A recent study, also by Annane and colleagues, in which hydrocortisone (a 50-mg intravenous bolus four times per day) and fludrocortisone (50  $\mu\text{g}$  per day) were administered for seven days to patients in septic shock showed improved survival in comparison with controls.<sup>97</sup> Combination therapy was beneficial even in patients with elevated base-line plasma cortisol levels if their serum cortisol level did not increase by more than 9  $\mu\text{g}$  per deciliter when stimulated by adrenocorticotrophic hormone. Somewhat worrisome was the fact that patients who did not have adrenal insufficiency and who received corticosteroids had a slight, albeit not statistically significant, trend toward increased mortality.<sup>98</sup> A second issue that has been raised is the high mortality rate in the population of patients — 63 percent in the placebo group. In summary, clinicians should not use high-dose corticosteroids in patients with sepsis. Low-dose hydrocortisone was effective in one study in patients with septic shock, but that finding has not been confirmed by other groups.

### AN EMERGING CONCEPT OF THE NATURE OF THE IMMUNE RESPONSE IN SEPSIS

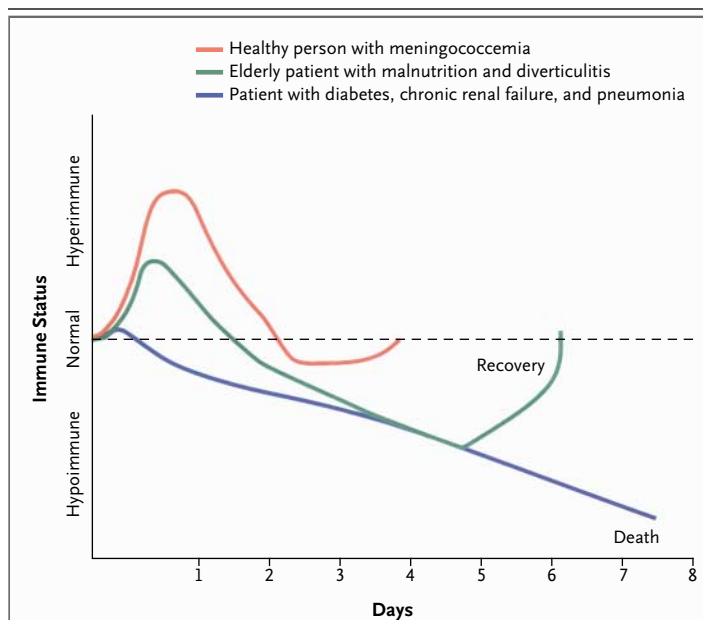
Our current hypothesis regarding the activity of the immune system during sepsis is illustrated in Figure 4, which depicts the responses of three hypothetical patients. The type of response is determined by many factors, including the virulence of the organism, the size of the inoculum, and the patient's coexisting conditions, nutritional status, age, and polymorphisms in cytokine genes or other immune-effector molecules or their receptors.

Our evaluation of spleens removed after the death of patients with sepsis demonstrated that the more prolonged the sepsis, the more profound was the loss of B cells and CD4 T cells.<sup>51</sup> Most deaths occurred during the prolonged hypoinflammatory state, and reversal or prevention of this immune deficiency should be a major focus of research. Antiinflammatory strategies applied early in patients with a hyperinflammatory immune response may be life-saving.<sup>13,14,29,78,84</sup> In addition to TNF- $\alpha$  and interleukin-1 $\beta$ , other inflammatory mediators may have critical roles in mediating cell injury in sepsis. Recently, high-mobility group 1 protein was identified as a late mediator of the lethality of endotoxin in mice and has correlated with outcome in patients with sepsis.<sup>99,100</sup>

Measurement of circulating concentrations of inflammatory mediators may prove to be useful in evaluating the stage of sepsis and in tailoring the administration of antiinflammatory agents. Alternatively, antiinflammatory agents used during the hypoinflammatory phase may worsen outcome.<sup>9,13,39</sup> When patients are determined to be in a hypoinflammatory state, inflammatory strategies that enhance the function of the innate or adaptive immune system may be found to be efficacious.<sup>15,39,43</sup> The ability of interferon- $\gamma$ , a potent macrophage activator, to improve survival in a subgroup of patients with sepsis may be the first example of immune-enhancing therapy for sepsis.<sup>41</sup> Interferon- $\gamma$  was found to restore macrophage HLA-DR expression and TNF- $\alpha$  production in patients with sepsis.

### POTENTIAL THERAPIES FOR SEPSIS

Diverse new agents have shown efficacy in clinically relevant animal models and offer hope as well as new insight into sepsis. O'Suilleabhain et al. noted that interleukin-12, a potent immune stimulant and



**Figure 4. Immunologic Response of Three Hypothetical Patients with Sepsis.**

The individual response is determined by many factors, including the virulence of the organism, the size of the inoculum, and the patient's coexisting conditions, age, and polymorphisms in genes for cytokines. The initial immune response is hyperinflammatory, but the response rapidly progresses to hypoinflammatory. A secondary bump in the hyperimmune state can occur during the hospital course with secondary infections. In the hypothetical healthy person who has contracted a serious meningococcal infection, there is an initial robust hyperinflammatory response. This patient would have extremely high plasma concentrations of TNF- $\alpha$  and other inflammatory cytokines. Death may occur due to a hyperinflammatory state, and antiinflammatory treatments may improve the likelihood of survival. If infection resolves rapidly, there is only a minimal hypoinflammatory state. In the hypothetical elderly malnourished person with diverticulitis, the initial response is limited, and, if infection persists, a prolonged hypoinflammatory response develops, followed by either recovery or death. In the hypothetical patient with diabetes, chronic renal failure, and pneumonia, the initial response is blunted, and there is prolonged depression of immune function, culminating in death.

Th1 inducer, reduced mortality from subsequent sepsis when administered after burn injury.<sup>101</sup> Administration of antibodies against complement-activation product C5a decreased the frequency of bacteremia, prevented apoptosis, and improved survival.<sup>102-104</sup> Calandra and associates reported that high concentrations of macrophage inhibitory factor were present in patients with sepsis and that the administration of antibodies against macrophage migration inhibitory factor protected mice from peritonitis.<sup>105</sup> Strategies that block apoptosis of lymphocytes or gastrointestinal epithelial cells have improved survival in experimental models of

sepsis.<sup>58-61,106,107</sup> Mice with sepsis that are deficient in poly-ADP-ribose polymerase 1 (PARP) have improved survival, and administration of a PARP inhibitor was beneficial in pig models.<sup>108,109</sup> The central nervous system is an important modulator of inflammation; electrical stimulation of the vagus nerve protects against endotoxic shock.<sup>110</sup> Thus, a variety of agents hold promise as effective new therapies for sepsis.

## CONCLUSIONS

A major shift has occurred in the way investigators view the problem of sepsis. Sepsis may not be attributable solely to an "immune system gone haywire" but may indicate an immune system that is severely compromised and unable to eradicate pathogens. Mechanisms of organ failure and death in patients with sepsis remain unknown, and autopsy studies do not reveal widespread necrosis. Current clinical

advances in the treatment of sepsis include therapy with activated protein C, tight control of blood glucose, and early goal-directed therapy to treat the cellular oxygen deficit. Future therapy may be directed at enhancing or inhibiting the patient's immune response, depending on genetic polymorphisms, the duration of disease, and the characteristics of the particular pathogen.

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