Elucidating how they become maladaptive and contribute to lethality remains a major challenge for sepsis research.

Organ Dysfunction and Shock As the body's responses to infection intensify, the mixture of circulating cytokines and other molecules becomes very complex: elevated blood levels of more than 60 molecules have been found in patients with septic shock. Although high concentrations of both pro- and anti-inflammatory molecules are found, the net mediator balance in the plasma of these extremely sick patients seems to be anti-inflammatory. For example, blood leukocytes from patients with severe sepsis are often hyporesponsive to agonists such as LPS. In patients with severe sepsis, persistence of leukocyte hyporesponsiveness has been associated with an increased risk of dying; at this time, the most predictive biomarker is a decrease in the expression of HLA-DR (class II) molecules on the surfaces of circulating monocytes, a response that seems to be induced by cortisol and/or IL-10. Apoptotic death of B cells, follicular dendritic cells, and CD4+ T lymphocytes also may contribute significantly to the immunosuppressive state.

ENDOTHELIAL INJURY Given the vascular endothelium's important roles in regulating vascular tone, vascular permeability, and coagulation, many investigators have favored widespread vascular endothelial injury as the major mechanism for multiorgan dysfunction. In keeping with this idea, one study found high numbers of vascular endothelial cells in the peripheral blood of septic patients. Leukocyte-derived mediators and platelet-leukocyte-fibrin thrombi may contribute to vascular injury, but the vascular endothelium also seems to play an active role. Stimuli such as TNF-α induce vascular endothelial cells to produce and release cytokines, procoagulant molecules, platelet-activating factor, nitric oxide, and other mediators. In addition, regulated cell-adhesion molecules promote the adherence of neutrophils to endothelial cells. Although these responses can attract phagocytes to infected sites and activate their antimicrobial arsenals, endothelial cell activation can also promote increased vascular permeability, microvascular thrombosis, DIC, and hypotension.

Tissue oxygenation may decrease as the number of functional capillaries is reduced by luminal obstruction due to swollen endothelial cells, decreased deformability of circulating erythrocytes, leukocyte-platelet-fibrin thrombi, or compression by edema fluid. On the other hand, studies using orthogonal polarization spectral imaging of the microcirculation in the tongue found that sepsis-associated derangements in capillary flow could be reversed by applying acetylcholine to the surface of the tongue or by giving nitroprusside intravenously; these observations suggest a neuroendocrine basis for the loss of capillary filling. Oxygen utilization by tissues may also be impaired by changes (possibly induced by nitric oxide) that decrease oxidative phosphorylation and ATP production while increasing glycolysis. The local accumulation of lactic acid, a consequence of increased glycolysis, may decrease extracellular pH and contribute to the slowdown in cellular metabolism that occurs within affected tissues.

Remarkably, poorly functioning "septic" organs usually appear normal at autopsy. There is typically very little necrosis or thrombosis, and apoptosis is largely confined to lymphoid organs and the gastrointestinal tract. Moreover, organ function usually returns to normal if patients recover. These points suggest that organ dysfunction during severe sepsis has a basis that is principally biochemical, not structural.

SEPTIC SHOCK The hallmark of septic shock is a decrease in peripheral vascular resistance that occurs despite increased levels of vasopressor catecholamines. Before this vasodilatory phase, many patients experience a period during which oxygen delivery to tissues is compromised by myocardial depression, hypovolemia, and other factors. During this "hypodynamic" period, the blood lactate concentration is elevated and central venous oxygen saturation is low. Fluid administration is usually followed by the hyperdynamic vasodilatory phase, during which cardiac output is normal (or even high) and oxygen consumption declines despite adequate oxygen delivery. The blood lactate level may be normal or increased, and normalization of central venous oxygen saturation may reflect improved oxygen delivery, decreased oxygen uptake by tissues, or left-to-right shunting.

Prominent hypotensive molecules include nitric oxide, β-endorphin, bradykinin, platelet-activating factor, and prostacyclin. Agents that inhibit the synthesis or action of each of these mediators can prevent or reverse endotoxic shock in animals. However, in clinical trials, neither a platelet-activating factor receptor antagonist nor a bradykinin antagonist improved survival rates among patients with septic shock, and a nitric oxide synthase inhibitor, L-N^G-methylarginine HCl, actually increased the mortality rate.

Severe Sepsis: A Single Pathogenesis? In some cases, circulating bacteria and their products almost certainly elicit multiorgan dysfunction and hypotension by directly stimulating inflammatory responses within the vasculature. In patients with fulminant meningococcemia, for example, mortality rates have correlated directly with blood levels of endotoxin and bacterial DNA and with the occurrence of DIC (Chap. 180). In most patients infected with other gram-negative bacteria, in contrast, circulating bacteria or bacterial molecules may reflect uncontrolled infection at a local tissue site and have little or no direct impact on distant organs; in these patients, inflammatory mediators or neural signals arising from the local site seem to be the key triggers for severe sepsis and septic shock. In a large series of patients with positive blood cultures, the risk of developing severe sepsis was strongly related to the site of primary infection: bacteremia arising from a pulmonary or abdominal source was eightfold more likely to be associated with severe sepsis than was bacteremic urinary tract infection, even after the investigators controlled for age, the kind of bacteria isolated from the blood, and other factors. A third pathogenesis may be represented by severe sepsis due to superantigen-producing *S. aureus* or *Streptococcus pyogenes*; the T cell activation induced by these toxins produces a cytokine profile that differs substantially from that elicited by gram-negative bacterial infection. Further evidence for different pathogenetic pathways has come from observations that the pattern of mRNA expression in peripheral-blood leukocytes from children with sepsis is different for gram-positive, gram-negative, and viral pathogens.

The pathogenesis of severe sepsis thus may differ according to the infecting microbe, the ability of the host's innate defense mechanisms to sense and respond to it, the site of the primary infection, the presence or absence of immune defects, and the prior physiologic status of the host. Genetic factors are probably important as well, yet despite much study very few allelic polymorphisms have been associated with sepsis severity in more than one or two analyses. Further studies in this area are needed.

CLINICAL MANIFESTATIONS

The manifestations of the septic response are superimposed on the symptoms and signs of the patient's underlying illness and primary infection. The rate at which severe sepsis develops may differ from patient to patient, and there are striking individual variations in presentation. For example, some patients with sepsis are normo- or hypothermic; the absence of fever is most common in neonates, in elderly patients, and in persons with uremia or alcoholism.

Hyperventilation, producing respiratory alkalosis, is often an early sign of the septic response. Disorientation, confusion, and other manifestations of encephalopathy may also develop early on, particularly in the elderly and in individuals with preexisting neurologic impairment. Focal neurologic signs are uncommon, although preexisting focal deficits may become more prominent.

Hypotension and DIC predispose to acrocyanosis and ischemic necrosis of peripheral tissues, most commonly the digits. Cellulitis, pustules, bullae, or hemorrhagic lesions may develop when hematogenous bacteria or fungi seed the skin or underlying soft tissue. Bacterial toxins may also be distributed hematogenously and elicit diffuse cutaneous reactions. On occasion, skin lesions may suggest specific pathogens. When sepsis is accompanied by cutaneous petechiae or purpura, infection with *N. meningitidis* (or, less commonly, *H. influenzae*) should be suspected (see Fig. 25e-42); in a patient who has been bitten by a tick while in an endemic area, petechial lesions also suggest Rocky Mountain spotted fever (see Fig. 211-1). A cutaneous lesion seen almost exclusively in neutropenic patients is ecthyma gangrenosum, often caused by *P. aeruginosa*. This bullous lesion surrounded by edema undergoes central hemorrhage and necrosis (see Fig. 189-1).