pathogenesis of sepsis thus depends, at least in part, on whether the bacterium's major signal molecule, LPS, can be sensed by the host.

Local and Systemic Host Responses to Invading Microbes Recognition of microbial molecules by tissue phagocytes triggers the production and/or release of numerous host molecules (cytokines, chemokines, prostanoids, leukotrienes, and others) that increase blood flow to the infected tissue (*rubor*), enhance the permeability of local blood vessels (*tumor*), recruit neutrophils and other cells to the site of infection (*calor*), and elicit pain (*dolor*). These reactions are familiar elements of local inflammation, the body's frontline innate immune mechanism for eliminating microbial invaders. Systemic responses are activated by neural and/or humoral communication with the hypothalamus and brainstem; these responses enhance local defenses by increasing blood flow to the infected area, augmenting the number of circulating neutrophils, and elevating blood levels of numerous molecules (such as the microbial recognition proteins discussed above) that have anti-infective functions.

CYTOKINES AND OTHER MEDIATORS Cytokines can exert endocrine, paracrine, and autocrine effects (Chap. 372e). TNF-α stimulates leukocytes and vascular endothelial cells to release other cytokines (as well as additional TNF-α), to express cell-surface molecules that enhance neutrophil endothelial adhesion at sites of infection, and to increase prostaglandin and leukotriene production. Whereas blood levels of TNF-α are not elevated in individuals with localized infections, they increase in most patients with severe sepsis or septic shock. Moreover, IV infusion of TNF-α can elicit fever, tachycardia, hypotension, and other responses. In animals, larger doses of TNF-α induce shock and death.

Although TNF-α is a central mediator, it is only one of many proinflammatory molecules that contribute to innate host defense. Chemokines, most prominently IL-8 and IL-17, attract circulating neutrophils to the infection site. IL-1β exhibits many of the same activities as TNF-α. TNF-α, IL-1β, interferon γ, IL-12, IL-17, and other proinflammatory cytokines probably interact synergistically with one another and with additional mediators. The nonlinearity and multiplicity of these interactions have made it difficult to interpret the roles played by individual mediators in both tissues and blood.

COAGULATION FACTORS Intravascular thrombosis, a hallmark of the local inflammatory response, may help wall off invading microbes and prevent infection and inflammation from spreading to other tissues. IL-6 and other mediators promote intravascular coagulation initially by inducing blood monocytes and vascular endothelial cells to express tissue factor (Chap. 78). When tissue factor is expressed on cell surfaces, it binds to factor VIIa to form an active complex that can convert factors X and IX to their enzymatically active forms. The result is activation of both extrinsic and intrinsic clotting pathways, culminating in the generation of fibrin. Clotting is also favored by impaired function of the protein C–protein S inhibitory pathway and depletion of antithrombin and proteins C and S, whereas fibrinolysis is reduced by increases in plasma levels of plasminogen activator inhibitor 1. Thus, there may be a striking propensity toward intravascular fibrin deposition, thrombosis, and bleeding; this propensity has been most apparent in patients with intravascular endothelial infections such as meningococcemia (Chap. 180). Evidence points to tissue factor–expressing microparticles derived from leukocytes as a potential trigger for intravascular coagulation. The contact system is activated during sepsis but contributes more to the development of hypotension than to that of disseminated intravascular coagulation (DIC).

Neutrophil extracellular traps (NETs) are produced when neutrophils, stimulated by microbial agonists or IL-8, release granule proteins and chromatin to form an extracellular fibrillar matrix. NETs kill bacteria and fungi with antimicrobial granule proteins (e.g., elastase) and histones. It has been reported that NETs can form within hepatic sinusoids in animals injected with large amounts of LPS, and platelets can induce NET formation without killing neutrophils. A role played by NETs in organ hypofunction during sepsis has been proposed but not established.

CONTROL MECHANISMS Elaborate control mechanisms operate within both local sites of inflammation and the systemic compartment.

Local control mechanisms Host recognition of invading microbes within subepithelial tissues typically ignites immune responses that rapidly kill the invaders and then subside to allow tissue recovery. The forces that put out the fire and clean up the battleground include molecules that neutralize or inactivate microbial signals. Among these molecules are intracellular factors (e.g., suppressor of cytokine signaling 3 and IL-1 receptor–associated kinase 3) that diminish the production of proinflammatory mediators by neutrophils and macrophages; anti-inflammatory cytokines (IL-10, IL-4); and molecules derived from essential polyunsaturated fatty acids (lipoxins, resolvins, and protectins) that promote tissue restoration. Enzymatic inactivation of microbial signal molecules (e.g., LPS) may be required to restore homeostasis; a leukocyte enzyme, acyloxyacyl hydrolase, has been shown to prevent prolonged inflammation in mice by inactivating LPS.

Systemic control mechanisms The signaling apparatus that links microbial recognition to cellular responses in tissues is less active in the blood. For example, whereas LPS-binding protein plays a role in recognizing LPS, in plasma it also prevents LPS signaling by transferring LPS molecules into plasma lipoprotein particles that sequester the lipid A moiety so that it cannot interact with cells. At the high concentrations found in blood, LPS-binding protein also inhibits monocyte responses to LPS, and the soluble (circulating) form of CD14 strips off LPS that has bound to monocyte surfaces.

Systemic responses to infection also diminish cellular responses to microbial molecules. Circulating levels of cortisol and anti-inflammatory cytokines (e.g., IL-6 and IL-10) increase even in patients with minor infections. Glucocorticoids inhibit cytokine synthesis by monocytes in vitro; the increase in blood cortisol levels that occurs early in the systemic response presumably plays a similarly inhibitory role. Epinephrine inhibits the TNF-α response to endotoxin infusion in humans while augmenting and accelerating the release of IL-10; prostaglandin E_2 has a similar "reprogramming" effect on the responses of circulating monocytes to LPS and other bacterial agonists. Cortisol, epinephrine, IL-10, and C-reactive protein reduce the ability of neutrophils to attach to vascular endothelium, favoring their demargination and thus contributing to leukocytosis while preventing neutrophil-endothelial adhesion in uninflamed organs. Studies in rodents have found that macrophage cytokine synthesis is inhibited by acetylcholine that is produced by choline acetyltransferase–secreting CD4+ T cells in response to stimulation by norepinephrine, whereas acetylcholine-producing B cells reduce neutrophil infiltration into tissues. Several lines of evidence thus suggest that the body's neuroendocrine responses to injury and infection normally prevent inflammation within organs distant from a site of infection. There is also evidence that these responses may be immunosuppressive.

IL-6 plays important roles in the systemic compartment. Released by many different cell types, IL-6 is an important stimulus to the hypothalamic-pituitary-adrenal axis, is the major procoagulant cytokine, and is a principal inducer of the acute-phase response, which increases the blood concentrations of numerous molecules that have anti-infective, procoagulant, or anti-inflammatory actions. Blood levels of IL-1 receptor antagonist often greatly exceed those of circulating IL-1β, for example, and this excess may inhibit the binding of IL-1β to its receptors. High levels of soluble TNF receptors neutralize TNF-α that enters the circulation. Other acute-phase proteins are protease inhibitors or antioxidants; these may neutralize potentially harmful molecules released from neutrophils and other inflammatory cells. Increased hepatic production of hepcidin (stimulated largely by IL-6) promotes the sequestration of iron in hepatocytes, intestinal epithelial cells, and erythrocytes; this effect reduces iron acquisition by invading microbes while contributing to the normocytic, normochromic anemia associated with inflammation.

It may thus be said that both local and systemic responses to infectious agents benefit the host in important ways. Most of these responses and the molecules responsible for them have been highly conserved during animal evolution and therefore may be adaptive.