intravenous fluids. Activated endothelium also upregulates production of nitric oxide (NO) and other vasoactive inflammatory mediators (e.g., C3a, C5a, and PAF), which may contribute to vascular smooth muscle relaxation and systemic hypotension.

- *Induction of a procoagulant state*. The derangement in coagulation is sufficient to produce the formidable complication of disseminated intravascular coagulation in up to half of septic patients. Sepsis alters the expression of many factors so as to favor coagulation. Pro-inflammatory cytokines increase tissue factor production by monocytes and possibly endothelial cells as well, and decrease the production of endothelial anti-coagulant factors, such as tissue factor pathway inhibitor, thrombomodulin, and protein C (see Fig. 4-6 and Fig. 4-8). They also dampen fibrinolysis by increasing plasminogen activator inhibitor-1 expression (see Fig. 4-6*B* and Fig. 4-8). The vascular leak and tissue edema decrease blood flow at the level of small vessels, producing stasis and diminishing the washout of activated coagulation factors. Acting in concert, these effects lead to systemic activation of thrombin and the deposition of fibrin-rich thrombi in small vessels, often throughout the body, further compromising tissue perfusion. In full-blown disseminated intravascular coagulation, the consumption of coagulation factors and platelets is so great that deficiencies of these factors appear, leading to concomitant bleeding and hemorrhage (Chapter 14).
- *Metabolic abnormalities*. Septic patients exhibit insulin resistance and hyperglycemia. Cytokines such as TNF and IL-1, stress-induced hormones (such as glucagon, growth hormone, and glucocorticoids), and catecholamines all drive gluconeogenesis. At the same time, the pro-inflammatory cytokines suppress insulin release while simultaneously promoting insulin resistance in the liver and other tissues, likely by impairing the surface expression of GLUT-4, a glucose transporter. Hyperglycemia decreases neutrophil function—thereby suppressing bactericidal activity—and causes increased adhesion molecule expression on endothelial cells. Although sepsis is initially associated with an acute surge in glucocorticoid production, this phase may be followed by adrenal insufficiency and a functional deficit of glucocorticoids. This may stem from depression of the synthetic capacity of intact adrenal glands or frank adrenal necrosis due to disseminated intravascular dissemination (*Waterhouse-Friderichsen syndrome*, Chapter 25). Finally, cellular hypoxia and diminished oxidative phosphorylation leads to increased lactate production and lactic acidosis.
- *Organ dysfunction*. Systemic hypotension, interstitial edema, and small vessel thrombosis all decrease the delivery of oxygen and nutrients to the tissues, which fail to properly utilize those nutrients that are delivered due to cellular hypoxia. High levels of cytokines and secondary mediators diminish myocardial contractility and cardiac output, and increased vascular permeability and endothelial injury can lead to the *acute respiratory distress syndrome* (Chapter 15). Ultimately, these factors may conspire to cause the failure of multiple organs, particularly the kidneys, liver, lungs, and heart, culminating in death.

The severity and outcome of septic shock are likely dependent upon the extent and virulence of the infection; the immune status of the host; the presence of other comorbid conditions; and the pattern and level of mediator production. The multiplicity of factors and the complexity of the interactions that underlie sepsis explain why most attempts to intervene therapeutically with antagonists of specific mediators have failed to be effective and may even have had deleterious effects in some cases. The standard of care remains antibiotics to treat the underlying infection and intravenous fluids, pressors and supplemental oxygen to maintain blood pressure and limit tissue hypoxia. Suffice it to say that even in the best of clinical centers, septic shock remains an obstinate clinical challenge.

It is worth mentioning here that an additional group of secreted bacterial proteins called *superantigens* also cause a syndrome similar to septic shock (e.g., *toxic shock syndrome*). Superantigens are polyclonal T-lymphocyte activators that induce the release of high levels of cytokines that result in a variety of clinical manifestations, ranging from a diffuse rash to vasodilation, hypotension, shock, and death.

Stages of Shock

Shock is a progressive disorder that, if uncorrected, leads to death. The exact mechanism(s) of death from sepsis are still unclear; aside from increased lymphocyte and enterocyte apoptosis there is only minimal cell death, and patients rarely have refractory hypotension, suggesting that organ failure secondary to edema and the attendant tissue hypoxia has a central role. For hypovolemic and cardiogenic shock, however, the pathways to death are reasonably well understood. Unless the insult is massive and rapidly lethal (e.g., a massive hemorrhage from a ruptured aortic aneurysm), shock in those settings tends to evolve through three general (albeit somewhat artificial) phases:

- An initial *nonprogressive phase* during which reflex compensatory mechanisms are activated and perfusion of vital organs is maintained
- A *progressive stage* characterized by tissue hypoperfusion and onset of worsening circulatory and metabolic imbalances, including lactic acidosis
- An *irreversible stage* that sets in after the body has incurred cellular and tissue injury so severe that even if the hemodynamic defects are corrected, survival is not possible

In the early nonprogressive phase of shock, a variety of *neurohumoral mechanisms* help to maintain cardiac output and blood pressure. These include baroreceptor reflexes, catecholamine release, activation of the renin-angiotensin axis, ADH release, and generalized sympathetic stimulation. The net effect is *tachycardia, peripheral vasoconstriction, and renal conservation of fluid*. Cutaneous vasoconstriction, for example, is responsible for the characteristic coolness and pallor of the skin in well-developed shock (although septic shock can initially cause cutaneous *vasodilation* and thus present with warm, flushed skin). Coronary and cerebral vessels are less sensitive to the sympathetic response and thus maintain relatively normal caliber, blood flow, and oxygen delivery.

If the underlying causes are not corrected, shock passes imperceptibly to the progressive phase, during which there