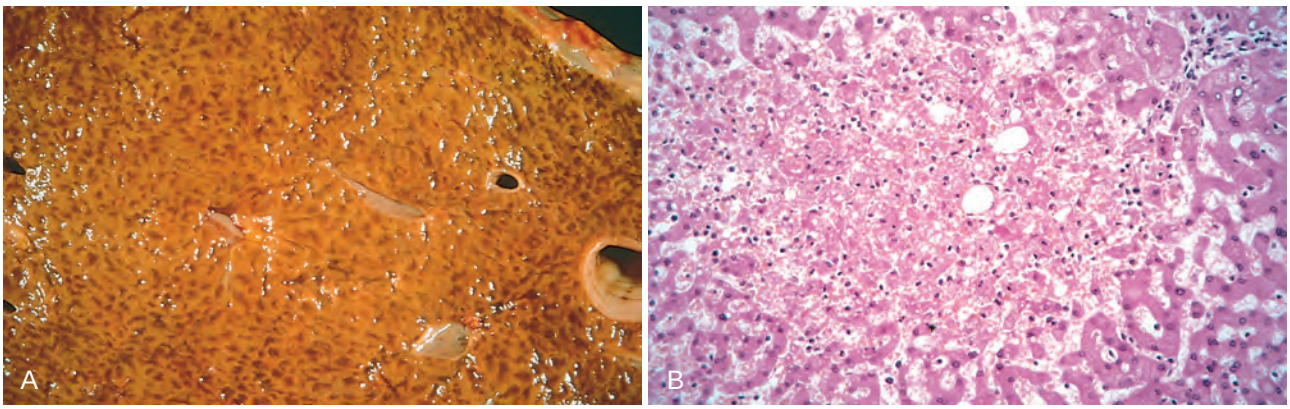

Figure 4-3 Liver with chronic passive congestion and hemorrhagic necrosis. **A,** Central areas are red and slightly depressed compared with the surrounding tan viable parenchyma, forming a "nutmeg liver" pattern (so-called because it resembles the cut surface of a nutmeg). **B,** Centrilobular necrosis with degenerating hepatocytes and hemorrhage. (Courtesy Dr. James Crawford, Department of Pathology, University of Florida, Gainesville, Fla.)

MORPHOLOGY

Congested tissues take on a dusky reddish-blue color (*cyanosis*) due to red cell stasis and the presence of deoxygenated hemoglobin. Microscopically, **acute pulmonary congestion** exhibits engorged alveolar capillaries, alveolar septal edema, and focal intraalveolar hemorrhage. In **chronic pulmonary congestion**, which is often caused by congestive heart failure, the septa are thickened and fibrotic, and the alveoli often contain numerous hemosiderin-laden macrophages called **heart failure cells**. In **acute hepatic congestion**, the central vein and sinusoids are distended. Because the centrilobular area is at the distal end of the hepatic blood supply, centrilobular hepatocytes may undergo ischemic necrosis while the periportal hepatocytes—better oxygenated because of proximity to hepatic arterioles—may only develop fatty change. In **chronic passive hepatic congestion**, the centrilobular regions are grossly red-brown and slightly depressed (because of cell death) and are accentuated against the surrounding zones of uncongested tan liver (**nutmeg liver**) (Fig. 4-3*A*). Microscopically, there is centrilobular hemorrhage, hemosiderin-laden macrophages, and variable degrees of hepatocyte dropout and necrosis (Fig. 4-3*B*).

Hemostasis, Hemorrhagic Disorders, and Thrombosis

Hemostasis can be defined simply as the process by which blood clots form at sites of vascular injury. Hemostasis is essential for life and is deranged to varying degrees in a broad range of disorders, which can be divided into two groups. In *hemorrhagic disorders*, characterized by excessive bleeding, hemostatic mechanisms are either blunted or insufficient to prevent abnormal blood loss. By contrast, in *thrombotic disorders* blood clots (often referred to as *thrombi*) form within intact blood vessels or within the chambers of the heart. As is discussed in Chapters 11 and 12, thrombosis has a central role in the most common and clinically important forms of cardiovascular disease.

While useful, it must be recognized that this division between bleeding and thrombotic disorders sometimes breaks down, in that generalized activation of clotting sometimes paradoxically produces bleeding due to the consumption of coagulation factors, as in *disseminated intravascular coagulation (DIC)*. To provide context for understanding disorders of bleeding and clotting, this discussion begins with normal hemostasis, focusing on the contribution of platelets, coagulation factors, and endothelium.

Hemostasis

Hemostasis is a precisely orchestrated process involving platelets, clotting factors, and endothelium that occurs at the site of vascular injury and culminates in the formation of a blood clot, which serves to prevent or limit the extent of bleeding. The general sequence of events leading to hemostasis at a site of vascular injury is shown in Figure 4-4.

- *Arteriolar vasoconstriction* occurs immediately and markedly reduces blood flow to the injured area (Fig. 4-4*A*). It is mediated by reflex neurogenic mechanisms and augmented by the local secretion of factors such as *endothelin*, a potent endothelium-derived vasoconstrictor. This effect is transient, however, and bleeding would resume if not for activation of platelets and coagulation factors.
- *Primary hemostasis: the formation of the platelet plug.* Disruption of the endothelium exposes subendothelial von Willebrand factor (vWF) and collagen, which promote platelet adherence and activation. Activation of platelets results in a dramatic shape change (from small rounded discs to flat plates with spiky protrusions that markedly increased surface area), as well as the release of secretory granules. Within minutes the secreted products recruit additional platelets, which undergo *aggregation* to form a *primary hemostatic plug* (Fig. 4-4*B*).
- *Secondary hemostasis: deposition of fibrin. Tissue factor* is also exposed at the site of injury. Tissue factor is a membrane-bound procoagulant glycoprotein that is normally expressed by subendothelial cells in the vessel wall, such as smooth muscle cells and fibroblasts. Tissue factor binds and activates factor VII (see later), setting in motion a cascade of reactions that culminates in *thrombin* generation. Thrombin cleaves circulating fibrinogen into insoluble *fibrin*, creating a fibrin meshwork, and also is a potent activator of platelets, leading to additional platelet aggregation at the site of injury. This sequence, referred to as *secondary hemostasis*, consolidates the initial platelet plug (Fig. 4-4*C*).
- *Clot stabilization and resorption.* Polymerized fibrin and platelet aggregates undergo contraction to form a solid,