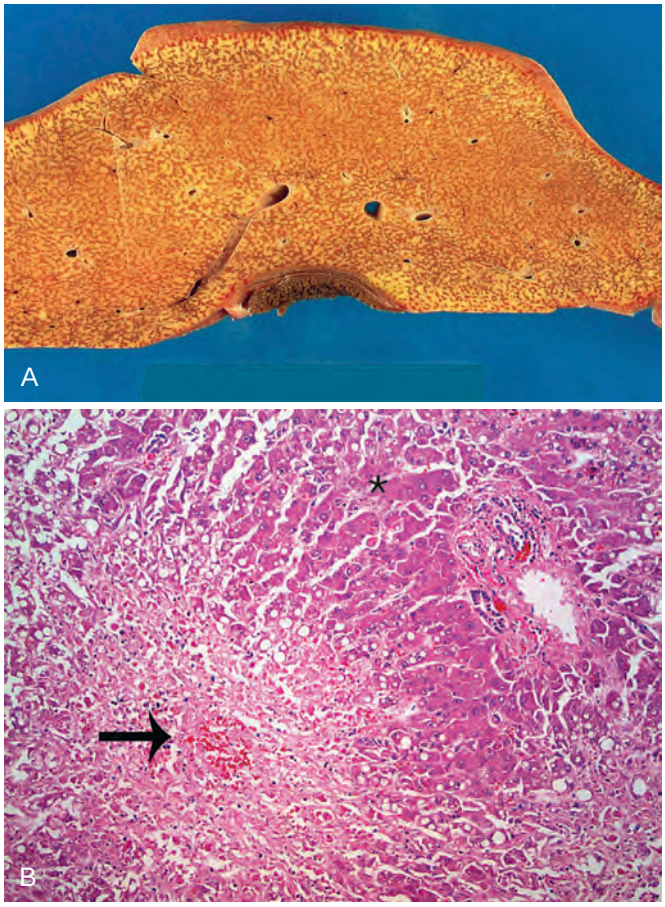

Figure 18-6 **A,** Massive necrosis, cut section of liver. The liver is small (700 g), bile-stained, soft, and congested. **B,** Hepatocellular necrosis caused by acetaminophen overdose. Confluent necrosis is seen in the perivenular region (zone 3) *(large arrow).* Residual normal tissue is indicated by the asterisk. (Courtesy Dr. Matthew Yeh, University of Washington, Seattle, Wash.)

these livers depends on the nature and duration of the insult. Toxic injuries, such as acetaminophen overdoses, usually take place within hours to days, too brief a period to allow time for scar formation or regeneration. Acute viral infections may cause failure over weeks to a few months, so that while hepatocyte injury continues to outpace repair, regeneration is often demonstrable. Also, this time scale allows for early scarring in areas of parenchymal loss.

Rarely, there may be diffuse poisoning of liver cells without obvious cell death and parenchymal collapse, such as in **diffuse microvesicular steatosis** related to fatty liver of pregnancy or idiosyncratic reactions to toxins (e.g., valproate, tetracycline). In these settings, usually related to primary mitochondrial dysfunction, hepatocytes are unable to perform their usual metabolic functions. In states of immunodeficiency, such as untreated infection with human immunodeficiency virus (HIV) or posttransplant immunosuppression, non-hepatotropic viruses, particularly cytomegalovirus, herpes simplex viruses, and adenovirus, can cause fulminant liver failure with histologic features specific to each of those viruses. With better treatments for HIV infection, these are declining as a cause of acute liver failure.

Clinical Course. **Acute liver failure manifests first with nausea, vomiting, and jaundice, followed by life-threatening encephalopathy, and coagulation defects.** Typically, serum liver transaminases are markedly elevated. The liver is initially enlarged due to hepatocyte swelling, inflammatory infiltrates, and edema; as parenchyma is destroyed, however, the liver shrinks dramatically. Decline of serum transaminases as the liver shrinks is often not, therefore, a sign of improvement, but is rather an indication that there are few viable hepatocytes left; this suspicion is confirmed if there is worsening jaundice, coagulopathy, and encephalopathy. With unabated progression, multiorgan system failure occurs and, if transplantation is not possible, death ensues. Other manifestations of acute liver failure are as follows:

- Alterations of bile formation and flow become clinically evident as yellow discoloration of the skin and sclera (*jaundice* and *icterus*, respectively) due to retention of bilirubin, and as *cholestasis* due to systemic retention of not only bilirubin but also other solutes eliminated in bile. Bilirubin metabolism and the pathophysiology of jaundice are discussed in detail later under cholestatic diseases. In the setting of acute liver failure, there is classic yellowing of skin, sclerae, and mucous membranes; cholestasis increases the risk of life-threatening bacterial infection.
- *Hepatic encephalopathy* is a spectrum of disturbances in consciousness, ranging from subtle behavioral abnormalities, to marked confusion and stupor, to deep coma and death. Encephalopathy may progress over days, weeks, or months following acute injury. Associated fluctuating, neurologic signs include rigidity and hyperreflexia. *Asterixis,* a particularly characteristic sign, is manifested as nonrhythmic, rapid extension-flexion movements of the head and extremities, best seen when the arms are held in extension with dorsiflexed wrists. Hepatic encephalopathy is regarded as a disorder of neurotransmission in the central nervous system and neuromuscular system. Elevated ammonia levels in blood and the central nervous system correlate with impaired neuronal function and cerebral edema.
- The liver is responsible for production of vitamin K-dependent and -independent clotting factors (Chapter 4). Thus, with massively impaired hepatic synthetic function, *coagulopathy* develops. Easy bruisability is an early sign of this process, which can lead to life-threatening or fatal intracranial bleeding. The liver is also responsible for helping to remove activated coagulation factors from the circulation, and loss of this function in some instances can lead to disseminated intravascular coagulation (Chapter 14), further exacerbating the bleeding tendency.
- *Portal hypertension* arises when there is diminished flow through the portal venous system, which may occur because of obstruction at the prehepatic, intrahepatic, or posthepatic level. While it can occur in acute live failure, portal hypertension is more commonly seen with chronic liver failure and is described later. In acute liver failure, if portal hypertension develops within days to weeks, obstruction is predominantly intrahepatic and the major clinical consequences are *ascites* and *hepatic encephalopathy*. In chronic liver disease, portal