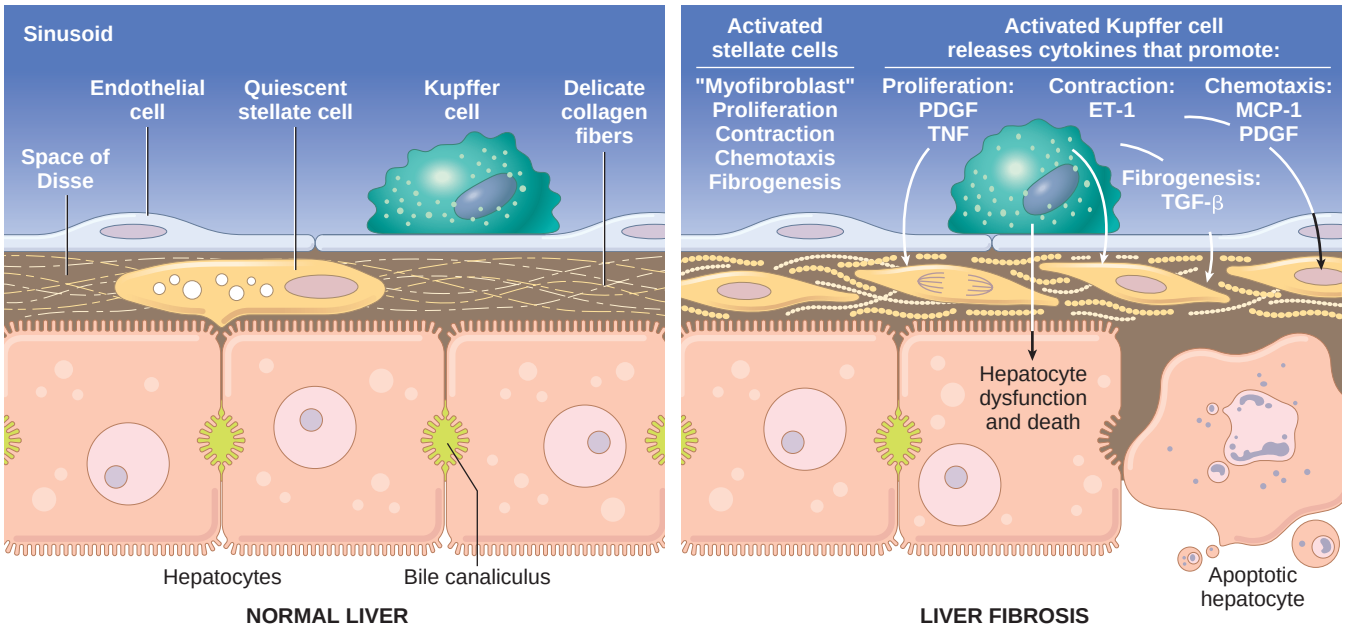

Figure 18-5 Stellate cell activation and liver fibrosis. Kupffer cell activation leads to secretion of multiple cytokines. Platelet-derived growth factor (PDGF) and tumor necrosis factor (TNF) activate stellate cells, and contraction of the activated stellate cells is stimulated by endothelin-1 (ET-1). Fibrosis is stimulated by transforming growth factor β (TGF-β). Chemotaxis of activated stellate cells to areas of injury is promoted by PDGF and monocyte chemotactic protein-1 (MCP-1). See text for details.

including, Kupffer cells and blood-derived dendritic cells, and presented to lymphocytes. Toll-like receptors detect host molecules, and also those derived from foreign invaders such as bacteria and viruses. These processes lead to elaboration of proinflammatory cytokines, which have diverse effects on the liver, including recruitment of inflammatory cells, hepatocyte injury, vascular disturbances, promotion of scarring, and perhaps even malignant transformation. Adaptive immunity plays an even more critical role in viral hepatitis. Antigen-specific and CD8+ T cells are involved in eradication of hepatitis B and C, the primary causes of chronic viral hepatitis, largely through elimination of infected hepatocytes. Lymphocytes, however, not only play a destructive role, but also help induce local hepatocyte replication through secretion of cytokines.

Liver Failure

The most severe clinical consequence of liver disease is liver failure. It may be the result of sudden and massive hepatic destruction, *acute liver failure*, which occurs in about 2000 people per year in the United States, or, more often, *chronic liver failure*, which follows upon years or decades of insidious, progressive liver injury. In some cases, individuals with chronic liver disease develop *acute-on-chronic liver failure*, in which an unrelated acute injury supervenes on a well-compensated late-stage chronic disease or the chronic disease itself has a flare of activity that leads directly to liver failure. Whatever the sequence, 80% to 90% of hepatic functional capacity must be lost before hepatic failure ensues. When the liver can no longer maintain homeostasis, transplantation offers the best hope for survival; the mortality rate in persons with hepatic failure without liver transplantation is about 80%.

Acute Liver Failure

Acute liver failure is defined as an acute liver illness associated with encephalopathy and coagulopathy that occurs within 26 weeks of the initial liver injury in the absence of pre-existing liver disease. Within this 26 week window, it is useful to know the interval between the onset of symptoms and liver failure, since this may provide helpful clues to the etiology as we shall describe below. Here we should clarify some terminology. Acute liver failure has been referred to as "fulminant liver failure" until recently. The term "acute liver failure" is preferred but since the older term remains entrenched in the literature, these terms are often used interchangeably. Acute liver failure is caused by *massive hepatic necrosis*, most often induced by drugs or toxins. Accidental or deliberate ingestion of acetaminophen (Chapter 9) accounts for almost 50% of cases in the United States, while autoimmune hepatitis, other drugs/toxins, and acute hepatitis A and B infections account for rest of cases. In Asia, acute hepatitis B and E predominate. With acetoaminophen toxicity, the liver failure occurs within a week of the onset of symptoms, whereas failure due to hepatitis viruses takes longer to develop. The mechanism of hepatocellular necrosis may be direct toxic damage (as with acetaminophen), but more often is a variable combination of toxicity and immune-mediated hepatocyte destruction (e.g., hepatitis virus infection).

MORPHOLOGY

Acute liver failure usually displays **massive hepatic necrosis**, with broad regions of parenchymal loss surrounding islands of regenerating hepatocytes (Fig. 18-6). These livers are small and shrunken. The prominence of scar and of ductular reactions in