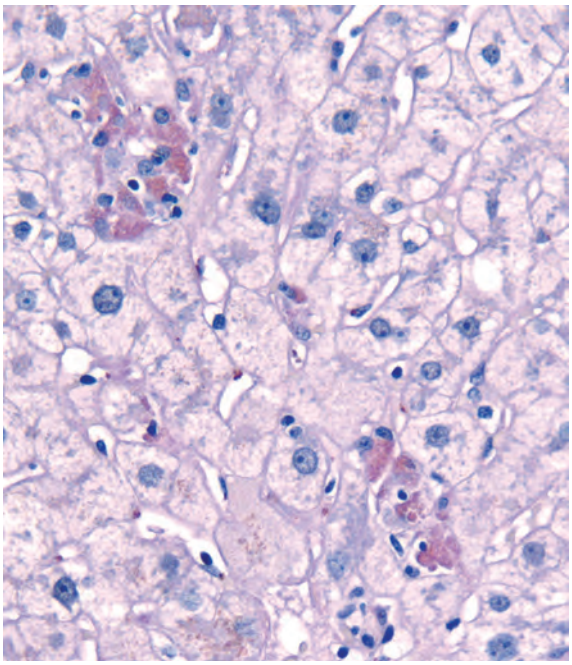

Figure 18-2 Acute hepatitis B. In this PAS-D stained slide, clusters of macrophages with eosinophilic cytoplasm indicate foci where hepatocytes have undergone necrosis. PAS-D, Periodic acid–Schiff after diastase digestion.

predominant mode of death in ischemic/hypoxic injury and a significant part of the response to oxidative stress.

Hepatocyte apoptosis is an active form of "programmed" cell death resulting in hepatocyte shrinkage, nuclear chromatin condensation (*pyknosis*), fragmentation (*karyorrhexis*), and cellular fragmentation into acidophilic *apoptotic bodies*. These changes are a result of caspase cascades described in detail in Chapter 2. Apoptotic hepatocytes were first clearly described in yellow fever by William Thomas Councilman and therefore have often been referred to as *Councilman bodies*; while apoptosis occurs in many forms of liver disease, by convention this eponym is restricted to that disease. In the more frequent settings in which apoptotic hepatocytes are seen, (e.g., acute and chronic hepatitis), the term *acidophil bodies* is used, due to their deeply eosinophilic staining characteristics (Fig. 18-3).

When there is widespread parenchymal loss there is often evidence of *confluent necrosis*, a severe, zonal loss of hepatocytes. This may be seen in acute toxic or ischemic injuries or in severe viral or autoimmune hepatitis. Confluent necrosis may begin as a zone of hepatocyte dropout around the central vein. The resulting space is filled by cellular debris, macrophages, and remnants of the reticulin meshwork. In *bridging necrosis* this zone may link central veins to portal tracts or bridge adjacent portal tracts (often with an inapparent central vein within the zone of injury). Even in diseases such as viral hepatitis in which hepatocytes are the principal targets of attack, vascular insults—via inflammation or thrombosis—lead to parenchymal extinction due to large areas of contiguous hepatocyte death (Fig. 18-4). The process depicted in Fig. 18-4 occurs in many types of liver diseases in which there is extensive hepatocyte loss and collapse of the supporting framework. The resultant cirrhosis is a common form of liver disease. In some cases there is scar regression as depicted in the figure and described in the next section.

Regeneration of lost hepatocytes occurs primarily by mitotic replication of hepatocytes adjacent to those that have died, even when there is significant confluent necrosis. *Hepatocytes are almost stem cell-like in their ability to continue to replicate even in the setting of years of chronic injury and thus stem cell replenishment is usually not a significant part of parenchymal repair.* In the most severe forms of acute liver failure, there is activation of the primary intrahepatic stem cell niche, namely the canal of Hering, but the contribution of stem cells to the replenishment of hepatocytes in such a setting setting remains unclear. Eventually, however, in many individuals with chronic disease the hepatocytes do reach replicative senescence and then there is clear evidence of stem cell activation seen in the form of *ductular reactions*. These duct like structures, sometimes without any lumens develop from stem cells and contribute significantly to parenchymal restoration. Interestingly, in biliary diseases, the "ductular" progeny of stem cells can give rise to cholangiocytes.

Scar Formation and Regression

The principal cell type involved in scar deposition is the hepatic stellate cell. In its quiescent form, it is a lipid (vitamin A) storing cell. However, in several forms of acute and chronic injury, the stellate cells can become activated and are converted into highly fibrogenic myofibroblasts. Proliferation of hepatic stellate cells and their activation into myofibroblasts is initiated by a series of changes that include an increase in the expression of platelet-derived growth factor receptor β (PDGFR-β) in the stellate cells. At the same time, Kupffer cells and lymphocytes release cytokines and chemokines that modulate the expression of genes in stellate cells that are involved in fibrogenesis. These, include transforming growth factor β (TGF-β) and its receptors, metalloproteinase 2 (MMP-2),

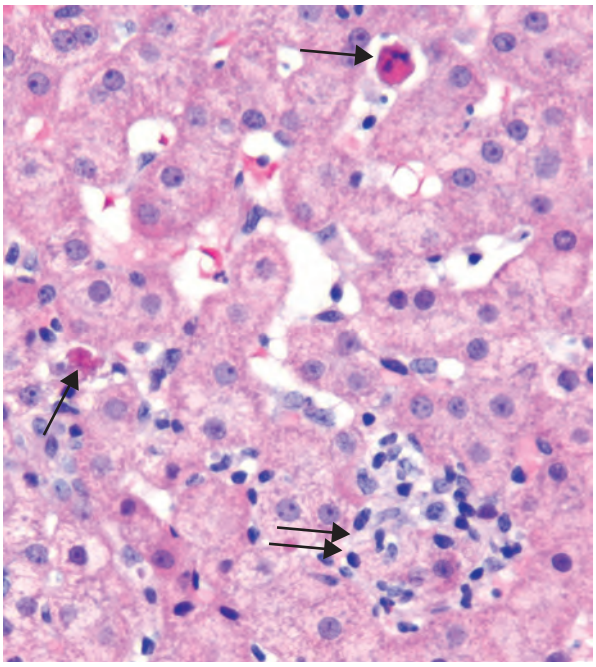

Figure 18-3 Foci of lobular hepatitis in chronic hepatitis C show apoptotic hepatocytes ("acidophil bodies"; *arrows*) and a focus of mononuclear infiltration surrounding a more darkly stained, injured hepatocyte (double arrows).