latter, these individuals constitute reservoirs for infection. In the case of HBV infection an older, but still often used term is the so called "healthy carrier". It is defined as an individual with HBsAg, without HBeAg, but with presence of anti-HBe; these patients have normal aminotransferases, low or undetectable serum HBV DNA, and a liver biopsy showing a lack of significant inflammation and necrosis (Fig. 18-11). In non-endemic areas such as the United States, between 5 and 10% of adults who acquire HBV infections become chronically infected, a very small number of whom become such "healthy carriers"; the rest have active disease, with consistent or intermittent signs and symptoms of active hepatitis, 20% of whom will go on to develop cirrhosis. In contrast, HBV infection acquired early in life in endemic areas (such as Southeast Asia, China, and Sub-Saharan Africa) gives rise to carrier states of the two types described above, in more than 90% of cases. It should be kept in mind that "healthy carrier" is probably not a stable state and that re-activation of hepatitis can occur in response to co-infection or alterations of immune function related to age or co-morbid diseases. Because of the confusion generated by the term "healthy carriers" many authorities prefer to use the term "inactive carrier".

HCV infection in the United States is quite different. Equivalent states to the HBV "healthy carrier" are not recognized. Acute HCV infection progresses to chronic hepatitis in 80% or more of infected individuals, one third of whom may progress to cirrhosis.

HIV and Chronic Viral Hepatitis. Because of the similar transmission mode and the similar high-risk patient population, co-infection of HIV and hepatitis viruses has become a common clinical problem. For example, in the United States, 10% of HIV-infected individuals are co-infected with HBV and 25% with HCV. In fact, chronic HBV and HCV infection are now leading causes of morbidity and mortality for HIV-infected individuals, even those who are on successful anti-HIV therapy. In individuals who are untreated or resistant to treatment and who therefore progress to acquired immunodeficiency syndrome (AIDS), liver disease is the second most common cause of death. It is clear that untreated HIV infection significantly exacerbates the severity of liver disease caused by HBV or HCV. In immunocompetent individuals with HIV infection, the differences in severity and progression of either HBV or HCV may not differ greatly from those who are HIV negative.

MORPHOLOGY

The general morphologic features of viral hepatitis are depicted schematically in Fig. 18-14. **The morphologic changes in acute and chronic viral hepatitis are shared among the hepatotropic viruses and can be mimicked by drug reactions or autoimmune hepatitis.**

Acute viral hepatitis. On gross inspection, livers involved by mild acute hepatitis appear normal or slightly mottled. At the other end of the spectrum, in massive hepatic necrosis the liver may shrink greatly as described earlier under acute liver failure (Fig. 18-6).

Microscopically, both acute and chronic hepatitis evoke a lymphoplasmacytic (mononuclear) infiltrate. Portal inflammation in acute hepatitis is minimal or absent. Most parenchymal injury is scattered throughout the hepatic lobule as "spotty necrosis" or **lobular hepatitis**. As described earlier, the hepatocyte injury may result in necrosis or apoptosis. In the former, the cytoplasm appears empty with only scattered wisps of cytoplasmic remnants. Eventually there is rupture of cell membranes leading to "dropout" of hepatocytes, leaving collapsed sinusoidal collagen reticulin framework behind; scavenger macrophages mark sites of dropout (Fig. 18-2). With apoptosis, hepatocytes shrink, becoming intensely eosinophilic, and their nuclei become pyknotic and fragmented; effector T cells may be present in the immediate vicinity (Figs. 18-3 and 18-14).

In severe acute hepatitis, confluent necrosis of hepatocytes is seen around central veins (Fig. 18-6*B*). In these areas there may be cellular debris, collapsed reticulin fibers, congestion/hemorrhage, and variable inflammation. With increasing severity, there is central-portal bridging necrosis, followed by, even worse, parenchymal collapse (Fig. 18-4*B*). In some cases massive hepatic necrosis and acute liver failure ensue, as described previously. In occasional cases, the injury is not severe enough to cause death (or necessitate transplantation), and the liver survives, although with abundant scarring, usually with replacement of areas of confluent necrosis. In such cases, some patients rapidly develop posthepatitic cirrhosis.

There is considerable morphologic overlap in acute hepatitis caused by various hepatotropic viruses. However, subtle differences may be seen, for example the mononuclear infiltrate in hepatitis A may be especially rich in plasma cells.

Chronic viral hepatitis. The defining histologic feature of chronic viral hepatitis is mononuclear portal infiltration. It may be mild to severe and variable from one portal tract to the next (Fig. 18-14). There is often **interface hepatitis** as well, in addition to lobular hepatitis, distinguished by its location at the interface between hepatocellular parenchyma and portal tract stroma. The hallmark of progressive chronic liver damage is scarring. At first, only portal tracts exhibit fibrosis, but in some patients, with time, fibrous septa—bands of dense scar—extend between portal tracts. In parallel with increasing scarring there is also increasing ductular reaction, reflecting stem cell activation. In the most severe cases, continued scarring and nodule formation leads to the development of cirrhosis as described earlier (Fig. 18-8).

Clinical assessment of chronic hepatitis often requires liver biopsy in addition to clinical and serologic data. Liver biopsy is helpful in confirming the clinical diagnosis, excluding common concomitant conditions (e.g., fatty liver disease, hemochromatosis), assessing histologic features associated with an increased risk of malignancy (e.g., small and large cell change, described later), grading the extent of hepatocyte injury and inflammation, and staging the progression of scarring. Histologic grading and staging of chronic hepatitis in liver biopsy specimens are often central to determinations of whether to treat the underlying disease.

A somewhat greater range of histologic features distinguish one viral infection from another in chronic hepatitis. In chronic hepatitis B, **"ground-glass" hepatocytes**—cells with endoplasmic reticulum swollen by HBsAg—is a diagnostic hallmark. Immunostaining can confirm the presence of viral antigen (Fig. 18-15). Chronic hepatitis C quite commonly shows lymphoid aggregates or fully formed lymphoid follicles (Fig. 18-16). Often, hepatitis C, particularly genotype 3, shows fatty change of scattered hepatocytes, although the infection may also cause systemic alterations leading to metabolic syndrome and, therefore,