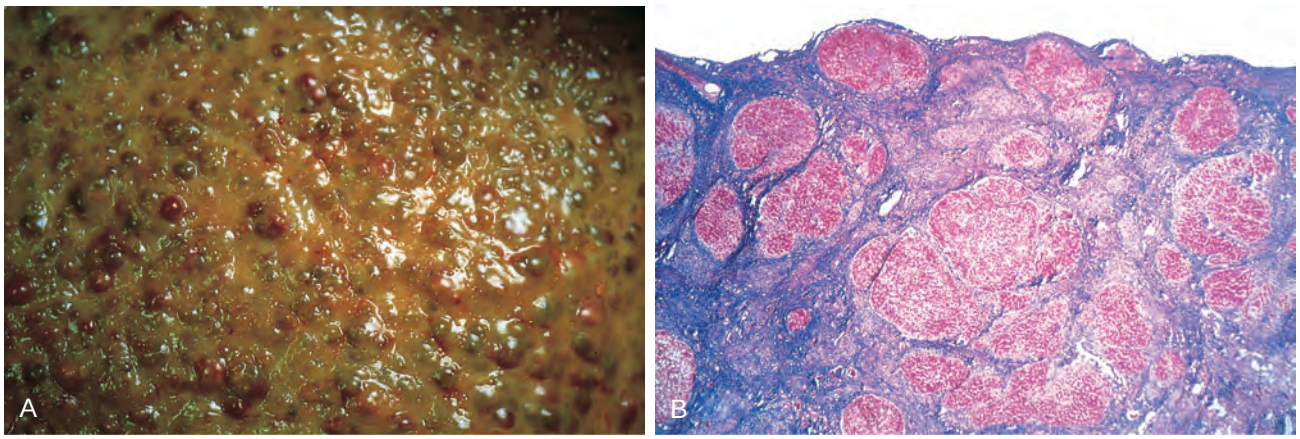

Figure 18-21 Alcoholic cirrhosis. **A,** The characteristic diffuse nodularity of the surface is induced by the underlying fibrous scarring. The average nodule size is 3 mm in this close-up view, typical of the "micronodular" cirrhosis of alcoholic liver disease. The greenish tint is caused by cholestasis. **B,** Microscopically, this cirrhosis is marked by small nodules entrapped in blue-staining fibrous tissue; fatty accumulation is no longer seen in this "burned out" stage. (Masson trichrome stain.)

- *Comorbid conditions.* Iron overload and infections with HCV and HBV synergize with alcohol, leading to increased severity of liver disease.

The pharmacokinetics and metabolism of alcohol are described in Chapter 9. Pertinent to this discussion are the detrimental effects of alcohol and its byproducts on hepatocellular function. *Exposure to alcohol causes steatosis, dysfunction of mitochondrial and cellular membranes, hypoxia, and oxidative stress.* At millimolar concentrations, alcohol directly affects microtubular and mitochondrial function and membrane fluidity.

Hepatocellular steatosis results from (1) shunting of normal substrates away from catabolism and toward lipid biosynthesis, as a result of increased generation of reduced nicotinamide adenine dinucleotide (NADH) by the two major enzymes of alcohol metabolism, alcohol dehydrogenase and acetaldehyde dehydrogenase; (2) impaired assembly and secretion of lipoproteins; and (3) increased peripheral catabolism of fat, thus releasing free fatty acids into the circulation.

The causes of alcoholic hepatitis are uncertain, but some of the factors that likely play important roles are discussed next. *Acetaldehyde* (the major intermediate metabolite of alcohol) induces lipid peroxidation and acetaldehyde-protein adduct formation, further disrupting cytoskeletal and membrane function. Cytochrome P-450 metabolism produces *reactive oxygen species* (ROS) that react with cellular proteins, damage membranes, and alter hepatocellular function. In addition, alcohol impairs hepatic metabolism of methionine, which *decreases glutathione levels,* thereby sensitizing the liver to oxidative injury. The induction of cytochrome P-450 enzymes in the liver by alcohol increases alcohol catabolism in the endoplasmic reticulum and enhances the conversion of other drugs (e.g., acetaminophen) to toxic metabolites. Alcohol causes the *release of bacterial endotoxin* from the gut into the portal circulation, inducing inflammatory responses in the liver, due to the activation of NF-κB, and release of TNF, IL-6, and TGF-α. In addition, alcohol stimulates the release of endothelins from sinusoidal endothelial cells, causing vasoconstriction and *contraction of activated, myofibroblastic stellate cells,* leading to a decrease in hepatic sinusoidal perfusion (already discussed under "Portal Hypertension").

Alcoholic liver disease, thus, is a chronic disorder featuring steatosis, hepatitis, progressive fibrosis, and marked derangement of vascular perfusion. In essence, alcoholic liver disease can be a regarded as a maladaptive state in which cells in the liver respond in an increasingly pathologic manner to a stimulus (alcohol) that originally was only marginally harmful.

Clinical Features. Hepatic steatosis may cause hepatomegaly, with mild elevation of serum bilirubin and alkaline phosphatase levels. Severe hepatic dysfunction is unusual. Alcohol withdrawal and the provision of an adequate diet are sufficient treatment. In contrast, alcoholic hepatitis tends to appear acutely, usually following a bout of heavy drinking. Symptoms and laboratory manifestations may range from minimal to those that mimic acute liver failure. Between these two extremes are the nonspecific symptoms of malaise, anorexia, weight loss, upper abdominal discomfort, and tender hepatomegaly, and the laboratory findings of hyperbilirubinemia, elevated serum aminotransferases and alkaline phosphatase, and often a neutrophilic leukocytosis. In contrast to other chronic liver diseases where serum ALT tends to be higher than serum AST, serum AST levels tend to be higher than serum ALT levels in a 2:1 ratio or higher in alcoholic liver disease. This can be helpful in differential diagnosis of chronic liver injury when adequate history is not available. An acute cholestatic syndrome may appear, resembling large bile duct obstruction.

The outlook is unpredictable; each bout of hepatitis incurs about a 10% to 20% risk of death. With repeated bouts, cirrhosis develops in about one third of patients within a few years. Alcoholic hepatitis also may be superimposed on established cirrhosis. With proper nutrition and total cessation of alcohol consumption, the alcoholic hepatitis may clear slowly. However, in some patients, the hepatitis persists, despite abstinence, and progresses to cirrhosis.