production of inflammatory cytokines such as TNF-α and IL-6. These changes in turn promote hepatocyte apoptosis. Fat laden cells are highly sensitive to lipid peroxidation products generated by oxidative stress which can damage mitochondrial and plasma membranes, causing apoptosis.

Diminished autophagy also contributes to mitochondrial injury and formation of Mallory-Denk bodies. Kupffer cell production of TNF-α and TGF-β activate stellate cells directly leading to deposition of scar tissue (Fig. 18-5). Stellate cell activation also occurs through the hedgehog signaling pathway in part through natural killer T-cell activation. In fact, the level of hedgehog pathway activity correlates with stage of fibrosis in NAFLD.

## MORPHOLOGY

**Pathologic steatosis is defined as involving more than 5% of hepatocytes.** Small, medium, and large droplets of fat, predominantly triglycerides, accumulate within hepatocytes just as they do in alcoholic steatosis. At the most clinically benign end of the spectrum, there is no appreciable hepatic inflammation, hepatocyte death, or scarring, despite persistent elevation of serum liver enzymes. **NASH almost completely overlaps in its histologic features with alcoholic hepatitis** (Fig. 18-22). In NASH, compared with alcoholic hepatitis, mononuclear cells may be more prominent than neutrophis and Mallory-Denk bodies are often less prominent. Steatofibrosis in NAFLD shows precisely the same features and progression as it does in alcoholic liver disease, although portal fibrosis may be more prominent. Cirrhosis may develop, is often subclinical for years, and, when established, the steatosis or steatohepatitis may be reduced or absent. **Greater than 90% of previously described "cryptogenic cirrhosis" (i.e., cirrhosis of unknown cause) is now thought to represent such "burned out" NAFLD.**

Pediatric NAFLD differs significantly from that seen in adults. Typically children show more diffuse steatosis, portal rather than central fibrosis, and portal and parenchymal mononuclear infiltration, rather than parenchymal neutrophils.

***Clinical Features.*** Clinical course of individuals with NAFLD/NASH are summarized in Figure 18-23. Individuals with simple steatosis are generally asymptomatic. Clinical presentation is often related to other signs and symptoms of the metabolic syndrome, in particular insulin resistance or diabetes mellitus. Imaging studies may reveal fat accumulation in the liver. However, liver biopsy is the most reliable diagnostic tool for NAFLD and NASH, and for assessment of scarring. Viral, autoimmune and other metabolic diseases of the liver must be excluded before the diagnosis can be made. Serum AST and ALT are elevated in about 90% of patients with NASH. Despite the enzyme elevations, patients may be asymptomatic. Others have general symptoms such as fatigue or right-sided abdominal discomfort caused by hepatomegaly. Because of the association between NASH and the metabolic syndrome, cardiovascular disease is a frequent cause of death in patients with NASH. The goal of treating individuals with NASH is to reverse the steatosis and prevent cirrhosis by correcting the underlying risk factors, such as obesity and hyperlipidemia, and to treat insulin resistance. NASH also increases the risk of hepatocellular carcinoma as do other metabolic diseases (discussed later).

## KEY CONCEPTS

### Nonalcoholic Fatty Liver Disease

- The most common metabolic disorder is nonalcoholic fatty liver disease, which is associated with the metabolic syndrome, obesity, type 2 diabetes mellitus or other impairments of insulin responsiveness, dyslipidemia, and hypertension.
- Nonalcoholic fatty liver disease may show all the changes associated with alcoholic liver disease: steatosis, steatohepatitis, and steatofibrosis, even though the features of steatohepatitis (e.g., hepatocyte ballooning, Mallory-Denk bodies, and neutrophilic infiltration) are often less prominent than they are in alcohol-related injury.

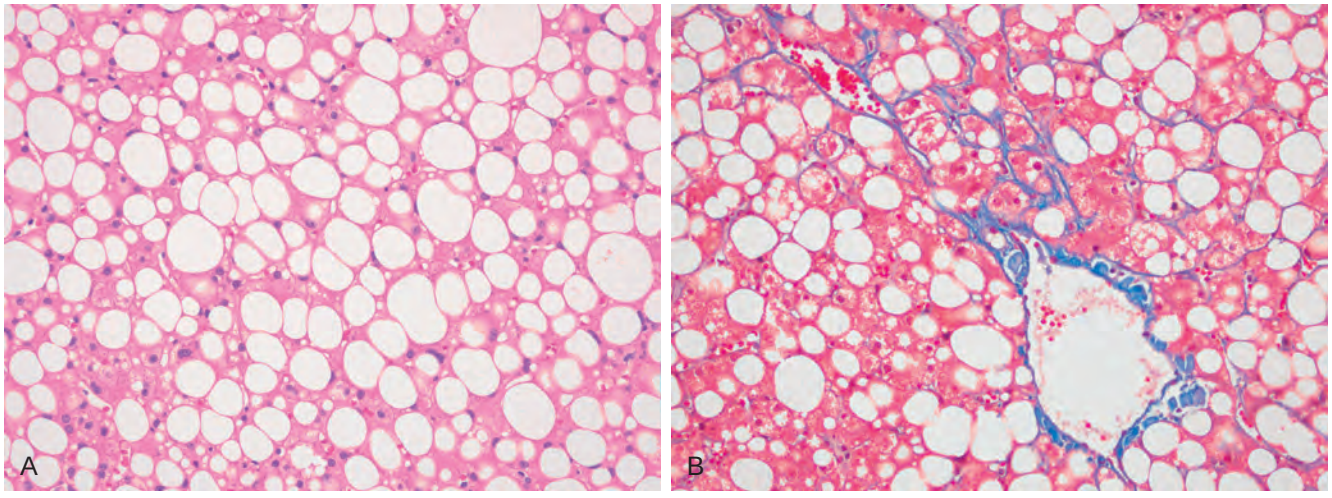


**Figure 18-22** Nonalcoholic fatty liver disease. **A,** Liver with mixed small and large fat droplets. **B,** Steatosis and steatofibrosis extending along sinusoids in a chicken wire fence pattern in which individual and clustered hepatocytes are surrounded by thin scars (blue fibers). Note the resemblance to alcoholic steatohepatitis depicted in Fig. 18-19. (Masson trichrome stain.)