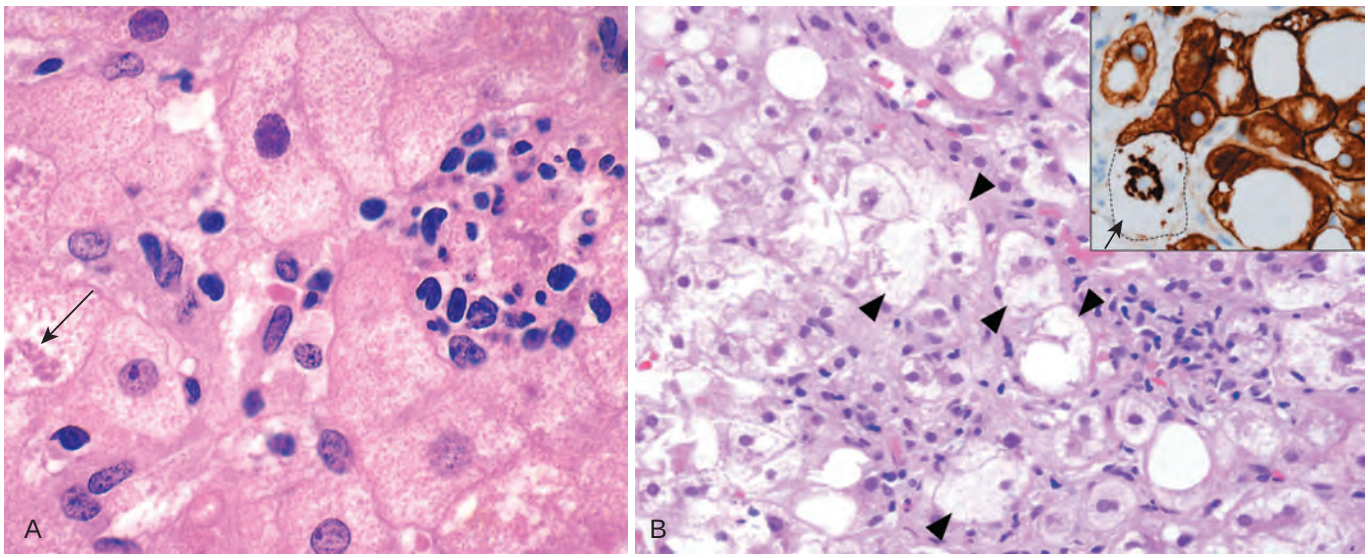

Figure 18-20 **A,** Alcoholic hepatitis with clustered inflammatory cells marking the site of a necrotic hepatocyte. A Mallory Denk body is present in another hepatocyte (arrow). **B,** Alcoholic steatohepatitis with many ballooned hepatocytes (arrowheads). Clusters of inflammatory cells are also present; inset shows immunostaining for keratins 8 and 18 (brown), with most hepatocytes, including those with fat vacuoles, showing normal cytoplasmic staining, but in the ballooned cell (arrow) the ubiquinated keratins are collapsed into the Mallory-Denk body, leaving the cytoplasm "empty." (Courtesy Dr. Elizabeth Brunt, Washington University, St. Louis, Mo.)

Alcoholic (Steato-) Hepatitis. Alcoholic hepatitis is characterized by:

1. Hepatocyte swelling and necrosis: Single or scattered foci of cells undergo swelling (ballooning) and necrosis (Fig. 18-20). The swelling results from the accumulation of fat and water, as well as proteins that are normally exported.

2. Mallory-Denk bodies: These are usually present as clumped, amorphous, eosinophilic material in ballooned hepatocytes. They are made up of tangled skeins of intermediate filaments such as keratins 8 and 18 in complex with other proteins such as ubiquitin (Fig. 18-20*B*). These inclusions are a characteristic but not specific feature of alcoholic liver disease, since they are also present in non-alcoholic fatty liver disease and in periportal distributions in Wilson disease and in chronic biliary tract diseases.

3. Neutrophilic reaction: Neutrophils permeate the hepatic lobule and accumulate around degenerating hepatocytes, particularly those having Mallory-Denk bodies. They may be more or less admixed with mononuclear cells (Fig. 18-20*B*).

Alcoholic steatofibrosis. Alcoholic hepatitis is often accompanied by prominent activation of sinusoidal stellate cells and portal fibroblasts, giving rise to fibrosis. Fibrosis begins with sclerosis of central veins. Perisinusoidal scar then accumulates in the space of Disse of the centrilobular region, spreading outward, encircling individual or small clusters of hepatocytes in a **chicken wire fence pattern** (Fig. 18-19). These webs of scar eventually link to portal tracts and then begin to condense into central-portal fibrous septa. With developing nodularity, cirrhosis becomes established. When alcohol use continues without interruption over the long term, the continual subdivision of established nodules by new webs of, perisinusoidal scarring leads to a classic micronodular or **Laennec cirrhosis** first described for end-stage alcoholic liver disease (Fig. 18-21). Early stages of scarring can regress with cessation of alcohol use, but the farther along toward cirrhosis the liver gets, the more vascular derangements prevent a full restoration of normal. Complete regression of alcoholic cirrhosis, while reported, is rare (Fig. 18-8).

Pathogenesis. Short-term ingestion of as much as 80 gm of alcohol (six beers or 8 ounces of 80-proof liquor) over one to several days generally produces mild, reversible hepatic steatosis. Daily intake of 80 gm or more of ethanol generates significant risk for severe hepatic injury, and daily ingestion of 160 gm or more for 10 to 20 years is associated more consistently with severe injury. *Only 10% to 15% of alcoholics, however, develop cirrhosis.* Thus, other factors must also influence the development and severity of alcoholic liver disease. These include:

- *Gender.* Women seem to be more susceptible to hepatic injury than men, although the majority of patients are men. This difference may be related to alcohol pharmacokinetics and metabolism, and the estrogen-dependent response to gut-derived endotoxin (LPS) in the liver. Although exact mechanisms are not known, it appears that estrogen increases gut permeability to endotoxins, which, in turn, increase the expression of the LPS receptor CD14 in Kupffer cells. This predisposes to increased production of proinflammatory cytokines and chemokines.
- *Ethnic and genetic differences.* In the United States, cirrhosis rates are higher for African American drinkers than for white Americans drinker. The difference cannot be explained by the amount of alcohol consumption, since there is no significant difference in consumption among the ethnic groups. Studies with twins suggest that there is a genetic component in alcohol-induced liver disease, although it remains difficult to separate genetic from environmental influences. Genetic polymorphisms in detoxifying enzymes and some cytokine promoters may play significant roles and contribute to ethnic differences. ALDH*2, a variant of aldehyde-dehydrogenase (ALDH), found in 50% of Asians, has a very low activity. Individuals homozygous for ALDH*2 are unable to oxidize acetaldehyde and do not tolerate alcohol, leading to alcohol intolerance characterized by upper body flushing and, variably, nausea or lethargy.