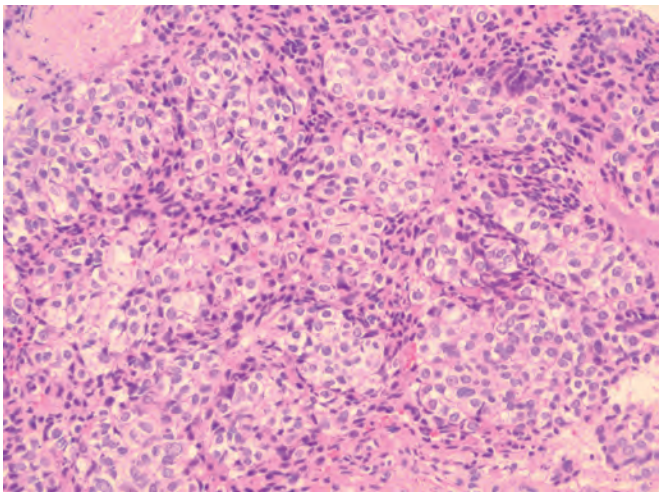

Figure 18-55 Hepatoblastoma. The photograph shows proliferating hepatoblasts consisting mostly of round "epithelial" type cells.

A characteristic feature of hepatoblastomas is the frequent activation of the WNT signaling pathway. This occurs by a variety of mechanisms involving mutations in molecules downstream of WNT signaling, including mutations in APC gene. Patients with Familial adenomatous polyposis frequently develop hepatoblastomas. Sporadic cases have activation of the beta-catenin signaling through other mechanisms. Chromosomal abnormalities are common in hepatoblastomas, and FOXG1, a regulator of the TGF-β pathway, is highly expressed in some tumors. Hepatoblastoma may be associated Beckwith-Wiedemann syndrome as well. The treatment is sugical resection and chemotherapy. Untreated, the tumor is usually fatal within a few years, but therapy has raised the 5-year survival to 80%.

Hepatocellular Carcinoma (HCC)

Worldwide, HCC (also known erroneously as *hepatoma*) accounts for approximately 5.4% of all cancers, but its incidence varies widely in different parts of the world. *More than 85% of cases occur in countries with high rates of chronic HBV infection.* The highest incidences of HCC are found in Asian countries (southeast China, Korea, Taiwan) and sub-Saharan African countries. In these locales, HBV is transmitted vertically and, as already discussed, the carrier state starts in infancy. The peak incidence of HCC in these areas is between 20 and 40 years of age, and in almost 50% of cases, the tumor appears in the absence of cirrhosis. As discussed later, many of these populations are exposed to aflatoxin, which is also a carcinogen (Chapter 7). The risk of HCC is decreasing in China, Singapore and Hong Kong, most likely due to institution of hepatitis B vaccination.

In Western counties, the incidence of HCC is rapidly increasing, largely owing to the hepatitis C epidemic. It tripled in the United States in recent decades, but it is still eightfold to 30-fold lower than the incidence in some Asian countries. In Western populations, HCC rarely manifests before the age of 60, and, in almost 90% of cases, the malignancy emerges after cirrhosis becomes established. There is a pronounced male preponderance throughout the world, about 3:1 in low-incidence areas and as high as 8:1 in high incidence areas. The reason for the gender imbalance is not known. Worldwide, liver cell cancer is the fifth leading cause of death in males.

Pathogenesis. **Chronic liver diseases are the most common setting for emergence of HCC.** While usually identified in a background of cirrhosis, cirrhosis per se is not a premalignant lesion. Indeed, cirrhosis is not required for hepatocarcinogenesis (Fig. 18-56). Rather, progression to cirrhosis and hepatocarcinogenesis take place *in parallel* over years to decades.

The most important underlying factors in hepatocarcinogenesis are viral infections (HBV, HCV) and toxic injuries (aflatoxin, alcohol). Thus where HBV and HCV are endemic, there is a very high incidence of HCC. Co-infection further increases risk. In Africa and Asia, aflatoxin, produced by *Aspergillus* species, is a mycotoxin that contaminates staple food crops. Aflatoxin metabolites are present in the urine of affected individuals as are aflatoxin-albumin adducts in serum. This helps to identify the populations at risk and confirm the important influence of

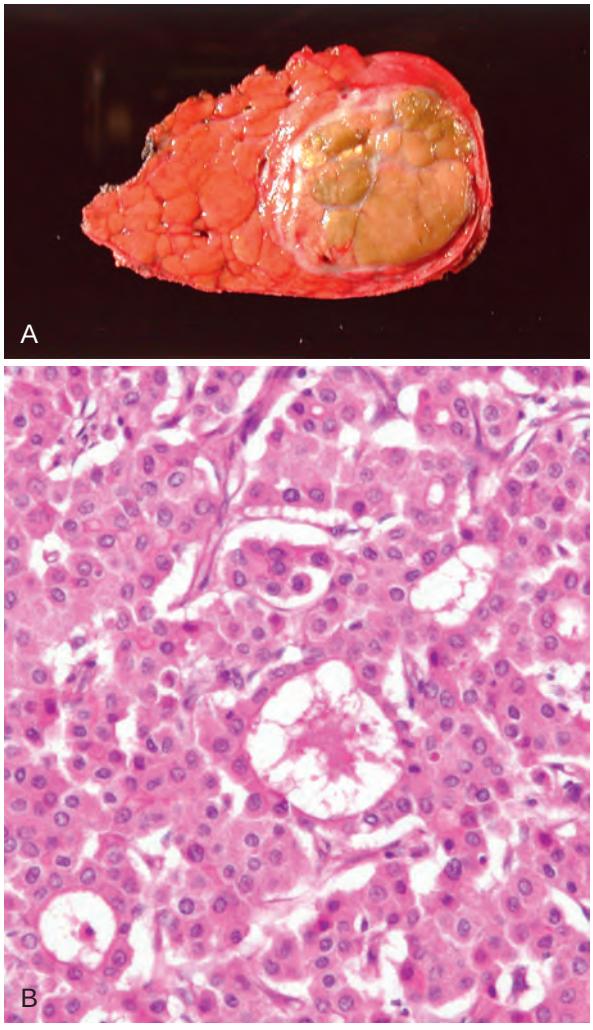

Figure 18-56 Hepatocellular carcinoma. **A,** Liver removed at autopsy showing a unifocal neoplasm replacing most of the right hepatic lobe. **B,** Malignant hepatocytes growing in distorted versions of normal architecture, including large pseudoacinar spaces (malformed, dilated bile canaliculi) and thickened hepatocyte trabeculae.