hepatitis C is characterized by portal-based fibrosis with bridging fibrosis and nodularity developing, ultimately culminating in the development of cirrhosis. In cirrhosis due to chronic hepatitis C, the liver is small and shrunken with characteristic features of a mixed micro- and macronodular cirrhosis seen on liver biopsy. In addition to the increased fibrosis that is seen in cirrhosis due to hepatitis C, an inflammatory infiltrate is found in portal areas with interface hepatitis and occasionally some lobular hepatocellular injury and inflammation. In patients with HCV genotype 3, steatosis is often present.

Similar findings are seen in patients with cirrhosis due to chronic hepatitis B. Of adult patients exposed to hepatitis B, about 5% develop chronic hepatitis B, and about 20% of those patients will go on to develop cirrhosis. Special stains for hepatitis B core (HBc) and hepatitis B surface (HBs) antigen will be positive, and ground-glass hepatocytes signifying hepatitis B surface antigen (HBsAg) may be present. In the United States, there are about 2 million carriers of hepatitis B, whereas in other parts of the world where hepatitis B virus (HBV) is endemic (i.e., Asia, Southeast Asia, sub-Saharan Africa), up to 15% of the population may be infected, having acquired the infection vertically at the time of birth. Thus, over 300–400 million individuals are thought to have hepatitis B worldwide. Approximately 25% of these individuals may ultimately develop cirrhosis.

Clinical Features and Diagnosis Patients with cirrhosis due to either chronic hepatitis C or B can present with the usual symptoms and signs of chronic liver disease. Fatigue, malaise, vague right upper quadrant pain, and laboratory abnormalities are frequent presenting features. Diagnosis requires a thorough laboratory evaluation, including quantitative HCV RNA testing and analysis for HCV genotype, or hepatitis B serologies to include HBsAg, anti-HBs, HBeAg (hepatitis B e antigen), anti-HBe, and quantitative HBV DNA levels.

TREATMENT CIRRHOSIS DUE TO CHRONIC VIRAL HEPATITIS B OR C

Management of complications of cirrhosis revolves around specific therapy for treatment of whatever complications occur (e.g., esophageal variceal hemorrhage, development of ascites and edema, or encephalopathy). In patients with chronic hepatitis B, numerous studies have shown beneficial effects of antiviral therapy, which is effective at viral suppression, as evidenced by reducing aminotransferase levels and HBV DNA levels, and improving histology by reducing inflammation and fibrosis. Several clinical trials and case series have demonstrated that patients with decompensated liver disease can become compensated with the use of antiviral therapy directed against hepatitis B. Currently available therapy includes lamivudine, adefovir, telbivudine, entecavir, and tenofovir. Interferon α can also be used for treating hepatitis B, but it should not be used in cirrhotics.

Treatment of patients with cirrhosis due to hepatitis C is a little more difficult because the side effects of pegylated interferon and ribavirin therapy are often difficult to manage. Dose-limiting cytopenias (platelets, white blood cells, red blood cells) or severe side effects can result in discontinuation of treatment. Nonetheless, if patients can tolerate treatment, and if it is successful, the benefit is great and disease progression is reduced. Recent studies have shown that if platelets are <100,000, albumin is <3.5 g/dL, and Model for End-Stage Liver Disease (MELD) score is >10, the risk of severe complications of interferon-based antiviral therapy is significant. Recent approval of Direct Acting Antivirals (DAAs) has led to improved efficacy of treatment with regimens that are safe and well tolerated.

CIRRHOSIS FROM AUTOIMMUNE HEPATITIS AND NONALCOHOLIC FATTY LIVER DISEASE

Other causes of posthepatitic cirrhosis include autoimmune hepatitis and cirrhosis due to nonalcoholic steatohepatitis. Many patients with autoimmune hepatitis (AIH) present with cirrhosis that is already established. Typically, these patients will not benefit from immunosuppressive therapy with glucocorticoids or azathioprine because the AIH is "burned out." In this situation, liver biopsy does not show a significant inflammatory infiltrate. Diagnosis in this setting requires positive autoimmune markers such as antinuclear antibody (ANA) or anti-smooth-muscle antibody (ASMA). When patients with AIH present with cirrhosis and active inflammation accompanied by elevated liver enzymes, there can be considerable benefit from the use of immunosuppressive therapy.

Patients with nonalcoholic steatohepatitis are increasingly being found to have progressed to cirrhosis. With the epidemic of obesity that continues in Western countries, more and more patients are identified with nonalcoholic fatty liver disease (Chap. 364). Of these, a significant subset has nonalcoholic steatohepatitis and can progress to increased fibrosis and cirrhosis. Over the past several years, it has been increasingly recognized that many patients who were thought to have cryptogenic cirrhosis in fact have nonalcoholic steatohepatitis. As their cirrhosis progresses, they become catabolic and then lose the telltale signs of steatosis seen on biopsy. Management of complications of cirrhosis due to either AIH or nonalcoholic steatohepatitis is similar to that for other forms of cirrhosis.

BILIARY CIRRHOSIS

Biliary cirrhosis has pathologic features that are different from either alcoholic cirrhosis or posthepatitic cirrhosis, yet the manifestations of end-stage liver disease are the same. Cholestatic liver disease may result from necroinflammatory lesions, congenital or metabolic processes, or external bile duct compression. Thus, two broad categories reflect the anatomic sites of abnormal bile retention: *intrahepatic* and *extrahepatic*. The distinction is important for obvious therapeutic reasons. Extrahepatic obstruction may benefit from surgical or endoscopic biliary tract decompression, whereas intrahepatic cholestatic processes will not improve with such interventions and require a different approach.

The major causes of chronic cholestatic syndromes are primary biliary cirrhosis (PBC), autoimmune cholangitis (AIC), primary sclerosing cholangitis (PSC), and idiopathic adulthood ductopenia. These syndromes are usually clinically distinguished from each other by antibody testing, cholangiographic findings, and clinical presentation. However, they all share the histopathologic features of chronic cholestasis, such as cholate stasis; copper deposition; xanthomatous transformation of hepatocytes; and irregular, so-called biliary fibrosis. In addition, there may be chronic portal inflammation, interface activity, and chronic lobular inflammation. Ductopenia is a result of this progressive disease as patients develop cirrhosis.

PRIMARY BILIARY CIRRHOSIS

PBC is seen in about 100–200 individuals per million, with a strong female preponderance and a median age of around 50 years at the time of diagnosis. The cause of PBC is unknown; it is characterized by portal inflammation and necrosis of cholangiocytes in small- and medium-sized bile ducts. Cholestatic features prevail, and biliary cirrhosis is characterized by an elevated bilirubin level and progressive liver failure. Liver transplantation is the treatment of choice for patients with decompensated cirrhosis due to PBC. A variety of therapies have been proposed, but ursodeoxycholic acid (UDCA) is the only approved treatment that has some degree of efficacy by slowing the rate of progression of the disease.

Antimitochondrial antibodies (AMA) are present in about 90% of patients with PBC. These autoantibodies recognize intermitochondrial membrane proteins that are enzymes of the pyruvate dehydrogenase complex (PDC), the branched-chain 2-oxoacid dehydrogenase complex, and the 2-oxogluterate dehydrogenase complex. Most relate to pyruvate dehydrogenase. These autoantibodies are not pathogenic but rather are useful markers for making a diagnosis of PBC.

Pathology Histopathologic analyses of liver biopsies of patients with PBC have resulted in identifying four distinct stages of the disease as it progresses. The earliest lesion is termed *chronic nonsuppurative*