smear) as well as measurements of the reticulocyte count, haptoglobin, lactate dehydrogenase (LDH), erythrocyte fragility, and Coombs' test as indicated.

Hepatic or Hepatocellular Jaundice

Typically, considerable reserve exists within the liver, so jaundice of hepatocellular origin can be indicative of significant injury or dysfunction. The differential diagnosis is broad because the liver is susceptible to many different forms of injury (Fig. 40-2). The most common categories are viral hepatitis, exposure to toxins (e.g., alcohol, carbon tetrachloride, amanita), prescription or nonprescription drugs, autoimmune disorders (e.g., autoimmune hepatitis, primary biliary cirrhosis [PBC], primary sclerosing cholangitis [PSC]), and liver tumors (mostly metastatic in origin). Impaired hepatic uptake of bilirubin can be a cause of unconjugated hyperbilirubinemia. When present, it is typically caused by competition for bilirubin uptake by drugs such as rifampin. Removal of the competing agent usually leads to resolution of the jaundice.

Impaired Conjugation

Another common cause of unconjugated hyperbilirubinemia is Gilbert's syndrome, a benign disorder that affects up to 7% of the population. This represents a normal variant that is not associated with intrinsic liver disease. Rather, it typically manifests during the second or third decade of life as mild unconjugated hyperbilirubinemia that is exacerbated by fasting or physical stress. Most of those affected have a total bilirubin level of less than 3 mg/dL, mostly of the unconjugated (indirect) fraction. The underlying genetic variant responsible is a homozygous abnormality in the TATAA element of the promoter region of the UDP-GT gene that results in lower enzymatic levels. The diagnosis is strongly suggested by unconjugated hyperbilirubinemia in the setting of normal hepatic enzyme levels, no known liver disease, and no evidence of hemolysis. Liver biopsy usually is not indicated, and therapy is not warranted. However, the bilirubin level does decrease significantly with phenobarbital administration. It is important to be aware of this common cause of unconjugated hyperbilirubinemia so that the patient can be reassured and more costly or invasive tests can be avoided.

Crigler-Najjar syndrome is another cause of unconjugated hyperbilirubinemia in which the bilirubin levels may be much higher due to a genetically determined decrease or absence of UDP-GT activity. Conjugation may also be impaired by mild, acquired defects of UDP-GT induced by drugs such as chloramphenicol.

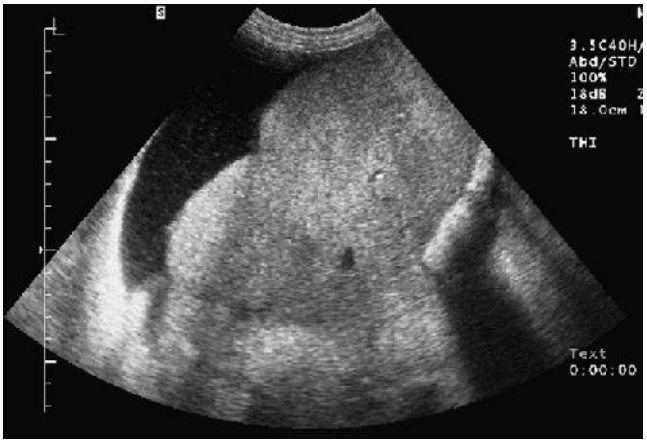

FIGURE 40-2 Ultrasound image shows a cirrhotic liver with atrophy, irregular contours, and ascites.

NEONATAL JAUNDICE

About 50% of term and 80% of preterm babies develop jaundice, which usually appears 2 to 4 days after birth and resolves spontaneously after 1 to 2 weeks. Most jaundice in newborn infants occurs for two main reasons. First, the enzymatic and transport pathways responsible for bilirubin metabolism are relatively immature and are unable to conjugate bilirubin as efficiently or as quickly as in adults. Second, bilirubin production is increased. Of those two mechanisms, the major defect is in bilirubin conjugation, which may cause mild to moderate unconjugated hyperbilirubinemia between the second and fifth days of life lasting until day 8 in normal births or about day 14 in premature births. This neonatal jaundice is usually harmless, and no specific therapy is required other than close observation.

More severe pathologic unconjugated hyperbilirubinemia can occur in neonates and usually is caused by a combination of hemolysis secondary to blood group incompatibility and defective conjugation. This neonatal jaundice is a serious condition that requires immediate attention because severe hyperbilirubinemia can lead to permanent neurologic damage (kernicterus). Phototherapy provided by conventional lighting or a fiberoptic light is the treatment of choice; it reduces neonatal jaundice (as assessed by serum bilirubin levels) compared with no treatment. Low-threshold compared with high-threshold phototherapy reduces neurodevelopmental impairment and hearing loss and reduces serum bilirubin on day 5 in infants with extremely low birth weight. However, it increases the duration of phototherapy, and it has no effect on mortality or on the rate of exchange transfusion. Close phototherapy, compared with distant light-source phototherapy, reduces the duration of phototherapy in infants with hyperbilirubinemia. If jaundice does not improve with phototherapy, other causes of neonatal jaundice should be assessed.

CONJUGATED HYPERBILIRUBINEMIA

Conjugated hyperbilirubinemia is associated with impaired formation or excretion of *all* components of bile, a situation termed *cholestasis.* The two major mechanisms of conjugated hyperbilirubinemia are defective excretion of bilirubin from hepatocytes into bile (intrahepatic cholestasis) and mechanical obstruction to the flow of bile through the bile ducts.

Impaired Hepatic Excretion (Intrahepatic Cholestasis)

Intrahepatic cholestasis can result from a wide range of conditions, including those that impair canalicular transport (e.g., certain drugs, circulating inflammatory cytokines during sepsis) and those that cause destruction of the small intrahepatic bile ducts. PBC, for example, is a chronic, progressive liver disease that occurs primarily in women and is characterized by the indolent destruction and subsequent disappearance over time of small lobular bile ducts. The gradual decrease in the number of bile ducts leads to progressive cholestasis, portal inflammation, fibrosis, and eventually cirrhosis. A similar loss of intrahepatic