Table 18-10 Major Causes of Neonatal Cholestasis

Bile duct obstruction
Extrahepatic biliary atresia
Neonatal infection
Cytomegalovirus
Bacterial sepsis
Urinary tract infection
Syphilis
Toxic
Drugs
Parenteral nutrition
Genetic disorders
Tyrosinemia
Niemann-Pick disease
Galactosemia
Defective bile acid synthetic pathways
α_1-Antitrypsin deficiency
Cystic fibrosis
Alagille syndrome (paucity of bile ducts)
Miscellaneous
Shock/hypoperfusion
Indian childhood cirrhosis
Idiopathic neonatal hepatitis

neonatal cholestasis should evoke a diligent search for recognizable toxic, metabolic, and infectious liver diseases (Table 18-10). With greater awareness of etiology and better diagnostic tools, *idiopathic neonatal hepatitis* constitutes only 10% to 15% of cases of neonatal hepatitis.

Differentiation of biliary atresia from nonobstructive neonatal cholestasis is very important, since definitive treatment of biliary atresia requires surgical intervention (Kasai procedure), whereas surgery may adversely affect the clinical course of a child with other disorders. Fortunately, discrimination can be made with clinical data in about 90% of cases, without liver biopsy. In 10% of cases, liver biopsy may be critical for distinguishing neonatal hepatitis from an identifiable cholangiopathy. Affected infants have jaundice, dark urine, light or acholic stools, and hepatomegaly. Variable degrees of hepatic synthetic dysfunction, such as hypoprothrombinemia, may be present.

MORPHOLOGY

The morphologic features of neonatal hepatitis (Fig. 18-34) include lobular disarray with focal liver cell apoptosis and necrosis. There is panlobular **giant-cell transformation** of hepatocytes; prominent hepatocellular and canalicular cholestasis; mild mononuclear infiltration of the portal areas; reactive changes in Kupffer cells; and extramedullary hematopoiesis. This predominantly parenchymal pattern of injury may blend imperceptibly into a ductal pattern of injury, with ductular reaction and fibrosis of portal tracts. In these cases distinction from an obstructive biliary atresia may therefore be difficult.

Biliary Atresia

Biliary atresia is defined as a complete or partial obstruction of the lumen of the extrahepatic biliary tree within the first 3 months of life. A major contributor to neonatal cholestasis, worthy of separate mention, it represents one third of infants with neonatal cholestasis. Although the definition for the disease is based on extrahepatic biliary obstruction, progressive inflammation and fibrosis are not necessarily confined to these locales; in some patients there is also progressive loss of intrahepatic ducts. Biliary atresia is the single most frequent cause of death from liver disease in early childhood and accounts for 50% to 60% of children referred for liver transplantation.

Pathogenesis. Two major forms of biliary atresia are recognized based on the presumed timing of luminal obliteration. The *fetal form* accounts for as many as 20% of cases and is commonly associated with other anomalies resulting from ineffective establishment of laterality of thoracic and abdominal organs during development. These include situs inversus malrotation of abdominal viscera, interrupted inferior vena cava, polysplenia, and congenital heart disease. The presumed cause is aberrant intrauterine development of the extrahepatic biliary tree.

Much more common is the *perinatal form* of biliary atresia, in which a presumed normally developed biliary tree is destroyed following birth. The etiology of perinatal biliary atresia remains unknown; viral infection and autoimmune reactions are leading suspects. Reovirus, rotavirus, and cytomegalovirus have been implicated in some cases. Biliary atresia with organ malformations has genetic basis.

MORPHOLOGY

The salient features of biliary atresia include **inflammation and fibrosing stricture of the hepatic or common bile ducts**; in some individuals, periductular inflammation also progresses into the intrahepatic bile ducts leading, additionally, to progressive destruction of the intrahepatic biliary tree. On liver biopsy, florid features of extrahepatic biliary obstruction as described earlier are evident in about two thirds of cases. In the remainder, inflammatory destruction of intrahepatic ducts leads to duct paucity, often without the accompanying ductular reactions, edema and neutrophils characteristic of obstruction. When biliary atresia is unrecognized or uncorrected, cirrhosis develops within 3 to 6 months of birth.

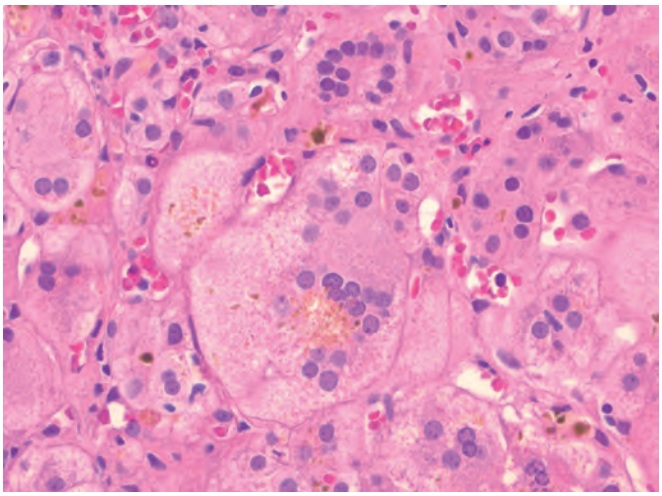

Figure 18-34 Neonatal hepatitis. Note the multinucleated giant hepatocytes.