ducts can occur as a result of chronic rejection after liver transplantation.

Drug-induced cholestasis is increasingly common, and immune-mediated or idiosyncratic mechanisms predominate. In some cases, there is associated hepatitis with significant cell injury. Representative drugs include, but are not limited to, nitrofurantoin, oral contraceptives, anabolic steroids, erythromycin, cimetidine, gold salts, chlorpromazine, prochlorperazine, imipramine, sulindac, tobutamide, ampicillin, and other penicillin-based antibiotics. Given the broad access to drugs is Western societies and the unpredictable nature of the adverse liver effects, a high index of suspicion for drug-induced cholestasis is required.

Intrahepatic cholestasis of pregnancy (ICP), also known as idiopathic jaundice of pregnancy, is a cholestatic disorder that is characterized by pruritus in the absence of a skin rash and elevation of aminotransferases (often up to 100 IU/L), alkaline phosphatase, 5-nucleotidase, and total and direct bilirubin concentrations. Total levels of bilirubin rarely exceed 6 mg/dL. The levels of γ-glutamyl transpeptidase are normal or only modestly elevated. ICP occurs in the second or third trimester of pregnancy and usually resolves spontaneously within 2 to 3 weeks after delivery. The diagnosis is suggested by the combination of pruritus and abnormal liver function tests with exclusion of other causes such as gallstones or intrinsic liver disease. ICP is associated with a higher risk for adverse perinatal outcome, including preterm birth, meconium passage, and fetal death.

The cause of ICP is not fully defined, but genetic, hormonal, and environmental factors are all likely to be involved. There is a high incidence of ICP in Chile and some other areas, and studies of potential genetic contributors are underway. Because adverse outcomes appear to occur predominantly after 37 weeks' gestation, management by an experienced obstetrics team and consideration of early delivery are warranted. Ursodeoxycholic acid may be effective in ameliorating maternal pruritus and improving liver function test results; however, no medication has yet been shown to reduce the risk to the fetus.

The hemophagocytic syndrome, also known as hemophagocytic lymphohystiocytosis (HLH), is an uncommon hyperinflammatory disorder caused by severe hypercytokinemia. It manifests as fever, splenomegaly, and jaundice, with hemophagocytosis in the bone marrow and other tissues pathologically. Primary or familial HLH, also called familial erythrophagocytic lymphohistiocytosis, is a heterogeneous autosomal recessive disorder that has been found to be more prevalent with parental consanguinity. Secondary HLH is associated with malignancy, immunodeficiency, and infection, especially viral infection. In HLH, there is an inherent defect of natural killer cells and cytotoxic T cells, so they are unable to cope effectively with the infectious agent or antigen. Liver biopsies in HLH reveal sinusoidal dilation with hemophagocytic histiocytosis.

Postoperative jaundice typically occurs 1 to 10 days after surgery and has an incidence of approximately 15% after heart surgery and 1% after elective abdominal surgery. It is multifactorial in origin, with increased bilirubin load from bleeding and blood transfusions as well as impaired bilirubin conjugation and secretion caused by inflammatory cytokines. It typically resolves fully over time. In hepatocellular disease, all three steps of hepatic bilirubin metabolism are impaired. Excretion, the rate-limiting step, is usually most affected, leading to predominantly conjugated hyperbilirubinemia.

Jaundice can be profound in acute hepatitis (see Chapter 41) without adverse prognostic implications. In chronic liver disease, however, persistent jaundice usually implies irreversible decrease in hepatic function and a poor prognosis.

Posthepatic Jaundice

Posthepatic jaundice, also called obstructive jaundice, results from a complete or partial obstruction of intrahepatic or extrahepatic bile ducts (Fig. 40-3 and E-Fig. 40-2). The most common causes are gallstones in the common bile duct and tumors of the pancreatic head. Not infrequently, the first sign of pancreatic cancer is jaundice. Other causes include strictures of the common bile duct resulting from prior surgery or passage of gallstones. Less common causes include congenital biliary atresia, pancreatitis, pancreatic pseudocysts, and parasites such as liver flukes (e.g., *Clonorchis sinensis*, *Dicrocoelium dendriticum*, *Opisthorchis viverrini*).

Mirizzi syndrome is an uncommon cause of posthepatic jaundice observed in 0.7% to 1.4% of patients after cholecystectomy.

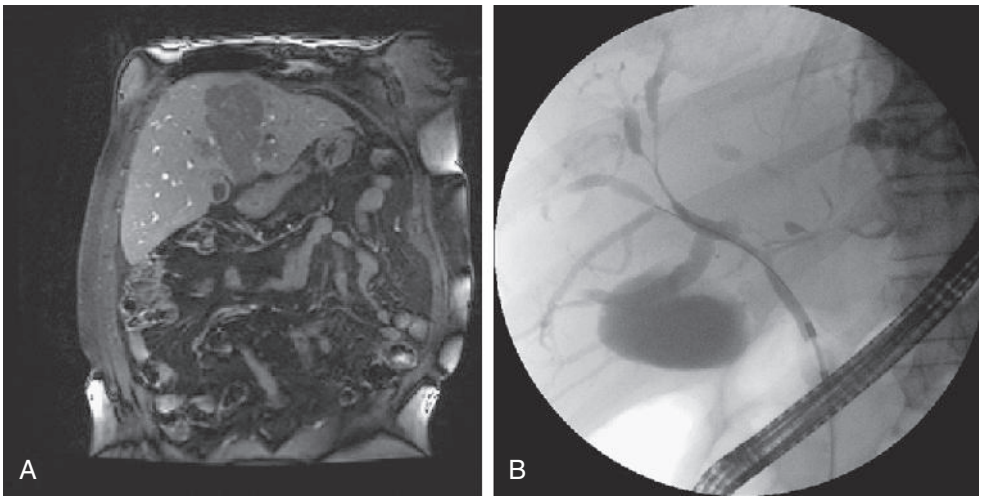

FIGURE 40-3 Hepatocellular carcinoma compressing the bile ducts. **A,** Sagittal view of computed abdominal tomography scan. **B,** Endoscopic retrograde cholangiopancreatography demonstrates multiple strictures of the bile ducts.