

The majority of cells in the liver are hepatocytes, which constitute two-thirds of the organ's mass. The remaining cell types are Kupffer cells (members of the reticuloendothelial system), stellate (Ito or fat-storing) cells, endothelial and blood vessel cells, bile ductular cells, and cells of supporting structures. Viewed by light microscopy, the liver appears to be organized in lobules, with portal areas at the periphery and central veins in the center of each lobule. However, from a functional point of view, the liver is organized into acini, with both hepatic arterial and portal venous blood entering the acinus from the portal areas (zone 1) and then flowing through the sinusoids to the terminal hepatic veins (zone 3); the intervening hepatocytes constitute zone 2. The advantage of viewing the acinus as the physiologic unit of the liver is that this perspective helps to explain the morphologic patterns and zonality of many vascular and biliary diseases not explained by the lobular arrangement.

Portal areas of the liver consist of small veins, arteries, bile ducts, and lymphatics organized in a loose stroma of supporting matrix and small amounts of collagen. Blood flowing into the portal areas is distributed through the sinusoids, passing from zone 1 to zone 3 of the acinus and draining into the terminal hepatic veins ("central veins"). Secreted bile flows in the opposite direction—i.e., in a counter-current pattern from zone 3 to zone 1. The sinusoids are lined by unique endothelial cells that have prominent fenestrae of variable sizes, allowing the free flow of plasma but not of cellular elements. The plasma is thus in direct contact with hepatocytes in the subendothelial space of Disse.

Hepatocytes have distinct polarity. The basolateral side of the hepatocyte lines the space of Disse and is richly lined with microvilli; it exhibits endocytotic and pinocytotic activity, with passive and active uptake of nutrients, proteins, and other molecules. The apical pole of the hepatocyte forms the canalicular membranes through which bile components are secreted. The canaliculi of hepatocytes form a fine network, which fuses into the bile ductular elements near the portal areas. Kupffer cells usually lie within the sinusoidal vascular space and represent the largest group of fixed macrophages in the body. The stellate cells are located in the space of Disse but are not usually prominent unless activated, when they produce collagen and matrix. Red blood cells stay in the sinusoidal space as blood flows through the lobules, but white blood cells can migrate through or around endothelial cells into the space of Disse and from there to portal areas, where they can return to the circulation through lymphatics.

Hepatocytes perform numerous and vital roles in maintaining homeostasis and health. These functions include the synthesis of most essential serum proteins (albumin, carrier proteins, coagulation factors, many hormonal and growth factors), the production of bile and its carriers (bile acids, cholesterol, lecithin, phospholipids), the regulation of nutrients (glucose, glycogen, lipids, cholesterol, amino acids), and the metabolism and conjugation of lipophilic compounds (bilirubin, anions, cations, drugs) for excretion in the bile or urine. Measurement of these activities to assess liver function is complicated by the multiplicity and variability of these functions. The most commonly used liver "function" tests are measurements of serum bilirubin, serum albumin, and prothrombin time. The serum bilirubin level is a measure of hepatic conjugation and excretion; the serum albumin level and prothrombin time are measures of protein synthesis. Abnormalities of bilirubin, albumin, and prothrombin time are typical of hepatic dysfunction. Frank liver failure is incompatible with life, and the functions of the liver are too complex and diverse to be subserved by a mechanical pump; a dialysis membrane; or a concoction of infused hormones, proteins, and growth factors.

LIVER DISEASES

While there are many causes of liver disease (Table 357-1), these disorders generally present clinically in a few distinct patterns and are usually classified as hepatocellular, cholestatic (obstructive), or mixed. In *hepatocellular diseases* (such as viral hepatitis and alcoholic liver disease), features of liver injury, inflammation, and necrosis predominate. In *cholestatic diseases* (such as gallstone or malignant obstruction, primary biliary cirrhosis, and some drug-induced liver

TABLE 357-1 LIVER DISEASES

Inherited hyperbilirubinemia	Liver involvement in systemic diseases
Gilbert's syndrome	Sarcoidosis
Crigler-Najjar syndrome, types I and II	Amyloidosis
Dubin-Johnson syndrome	Glycogen storage diseases
Rotor syndrome	Celiac disease
Viral hepatitis	Tuberculosis
Hepatitis A	<i>Mycobacterium avium-intracellulare</i> infection
Hepatitis B	Cholestatic syndromes
Hepatitis C	Benign postoperative cholestasis
Hepatitis D	Jaundice of sepsis
Hepatitis E	Total parenteral nutrition-induced jaundice
Others (Epstein-Barr virus [mononucleosis] herpesvirus, adenovirus hepatitis)	Cholestasis of pregnancy
Cryptogenic hepatitis	Cholangitis and cholecystitis
Immune and autoimmune liver diseases	Extrahepatic biliary obstruction (stone, stricture, cancer)
Primary biliary cirrhosis	Biliary atresia
Autoimmune hepatitis	Caroli's disease
Sclerosing cholangitis	Cryptosporidiosis
Overlap syndromes	Drug-induced liver disease
Graft-versus-host disease	Hepatocellular patterns (isoniazid, acetaminophen)
Allograft rejection	Cholestatic patterns (methyltestosterone)
Genetic liver diseases	Mixed patterns (sulfonamides, phenytoin)
α ₁ -Antitrypsin deficiency	Micro- and macrovesicular steatosis (methotrexate, fialuridine)
Hemochromatosis	Vascular injury
Wilson's disease	Veno-occlusive disease
Benign recurrent intrahepatic cholestasis	Budd-Chiari syndrome
Progressive familial intrahepatic cholestasis, types I–III	Ischemic hepatitis
Others (galactosemia, tyrosinemia, cystic fibrosis, Newman-Pick disease, Gaucher's disease)	Passive congestion
Alcoholic liver disease	Portal vein thrombosis
Acute fatty liver	Nodular regenerative hyperplasia
Acute alcoholic hepatitis	Mass lesions
Laënnec's cirrhosis	Hepatocellular carcinoma
Nonalcoholic fatty liver	Cholangiocarcinoma
Steatosis	Adenoma
Steatohepatitis	Focal nodular hyperplasia
Acute fatty liver of pregnancy	Metastatic tumors
	Abscess
	Cysts
	Hemangioma

diseases), features of inhibition of bile flow predominate. In a mixed pattern, features of both hepatocellular and cholestatic injury are present (such as in cholestatic forms of viral hepatitis and many drug-induced liver diseases). The pattern of onset and prominence of symptoms can rapidly suggest a diagnosis, particularly if major risk factors are considered, such as the age and sex of the patient and a history of exposure or risk behaviors.

Typical presenting symptoms of liver disease include jaundice, fatigue, itching, right-upper-quadrant pain, nausea, poor appetite, abdominal distention, and intestinal bleeding. At present, however, many patients are diagnosed with liver disease who have no symptoms and who have been found to have abnormalities in biochemical liver tests as a part of a routine physical examination or screening for blood