CHAPTER

28

Alterations in Hepatobiliary Function

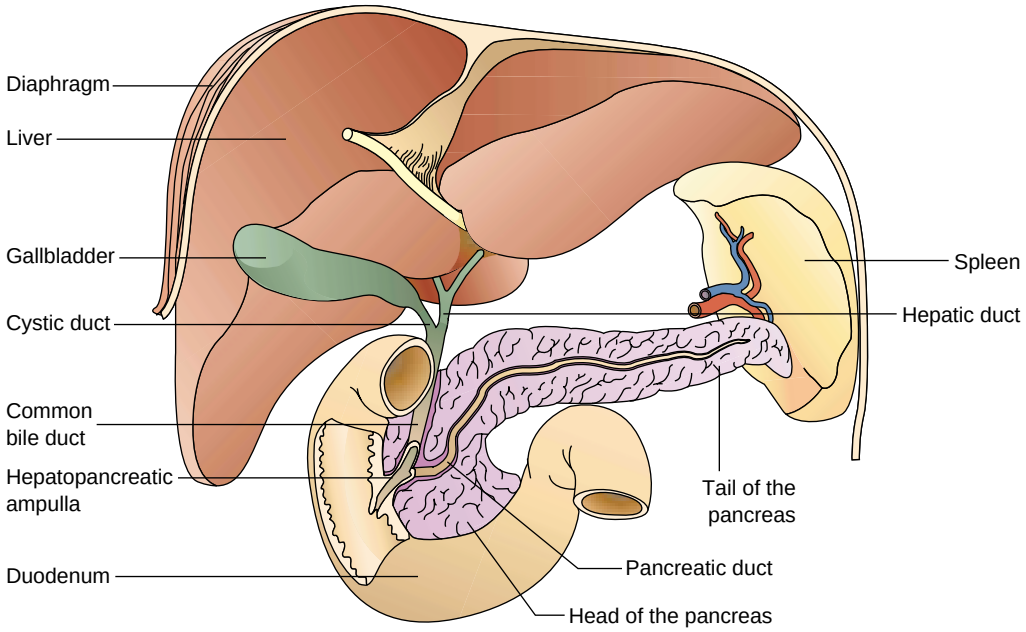
The liver, the gallbladder, and the exocrine pancreas are classified as accessory organs of the gastrointestinal tract. In addition to producing digestive secretions, the liver and the pancreas have other important functions. For example, the endocrine pancreas supplies the insulin and glucagon needed in cell metabolism, whereas the liver synthesizes glucose, plasma proteins, and blood clotting factors and is responsible for the degradation and elimination of drugs and hormones, among other functions. This chapter focuses on functions and disorders of the liver, the biliary tract and gallbladder, and the exocrine pancreas.

THE LIVER AND HEPATOBILIARY SYSTEM

The liver is the largest visceral organ in the body, weighing approximately 1.3 kg (3 lb) in the adult (Fig. 28-1). It lies below and on the right side of the diaphragm. Except for the portion that is in the epigastric area, the liver is contained within the rib cage and in healthy persons cannot normally be palpated. The liver is surrounded by a tough fibroelastic capsule called *Glisson's capsule*.

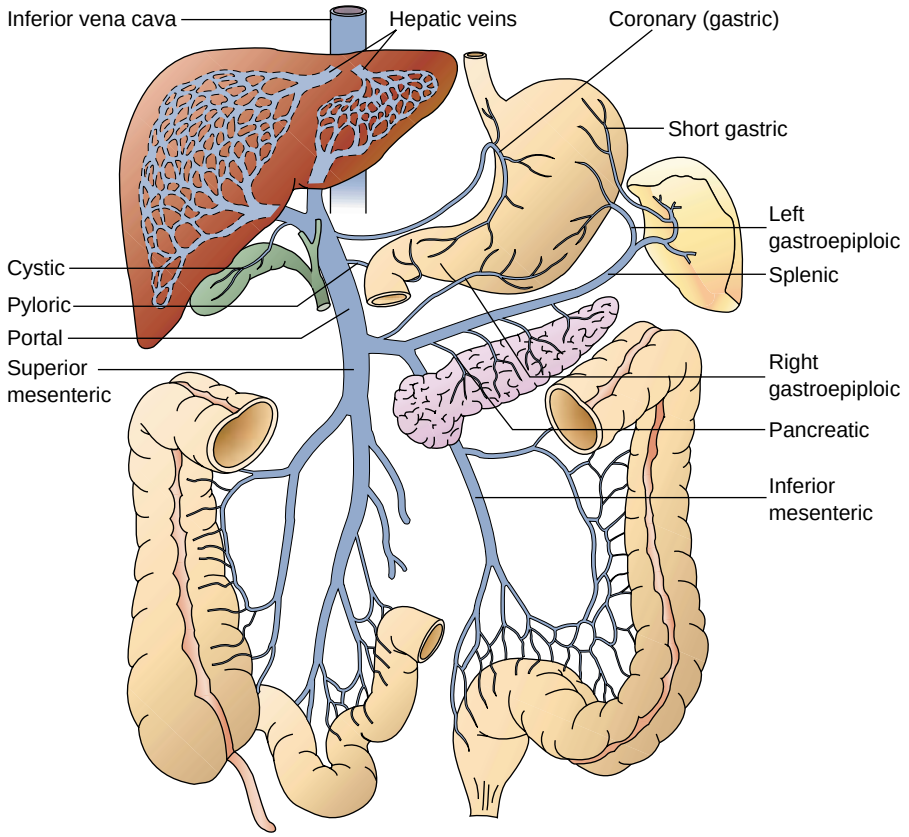
The liver is unique among the abdominal organs in having a dual blood supply—the *hepatic artery* and the *portal vein*. Approximately 300 mL of blood per minute enters the liver through the hepatic artery; another 1050 mL/minute enters by way of the valveless portal vein, which carries blood from the stomach, the small and the large intestines, the pancreas, and the spleen[1] (Fig. 28-2). Although the blood from the portal vein is incompletely saturated with oxygen, it supplies approximately 60% to 70% of the oxygen needs of the liver. The venous outflow from the liver is carried by the valveless hepatic veins, which empty into the inferior vena cava just below the level of the diaphragm. The pressure difference between the hepatic vein and the portal vein normally is such that the liver stores approximately 450 mL of blood.[1] This blood can be shifted back into the general circulation during periods of hypovolemia and shock. In congestive heart failure, in which the pressure in the vena cava increases, blood backs up and accumulates in the liver.

The *lobules* are the functional units of the liver. Each lobule is a cylindrical structure that measures approximately 0.8 to

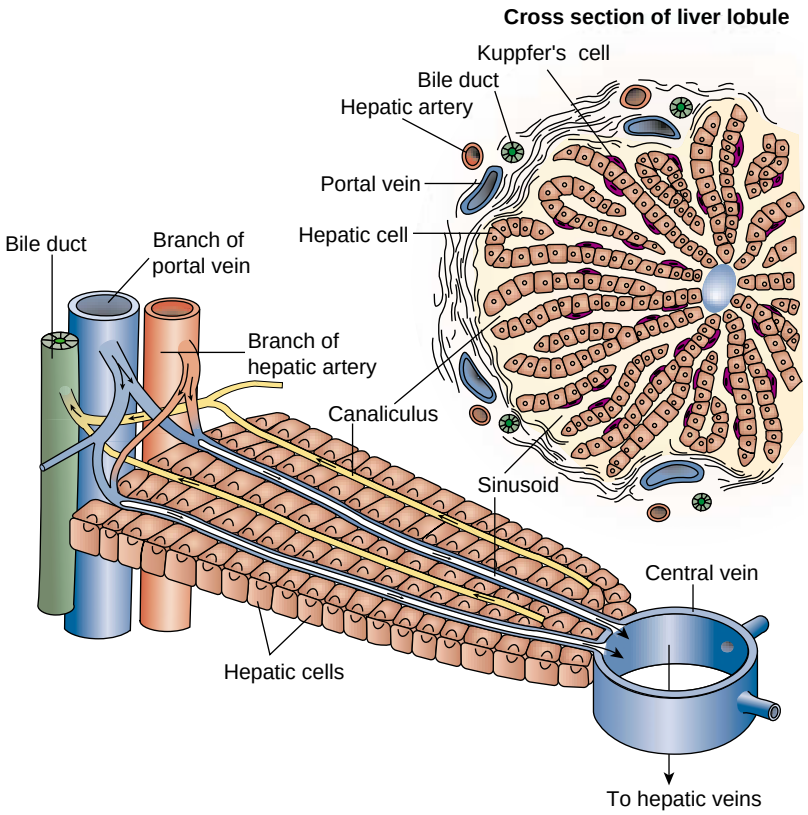


■ **FIGURE 28-1** ■ The liver and biliary system, including the gallbladder and bile ducts.

2 mm in diameter and several millimeters long. There are approximately 50,000 to 100,000 lobules in the liver.[1] Each lobule is organized around a central vein that empties into the hepatic veins and from there into the vena cava. The terminal bile ducts and small branches of the portal vein and hepatic artery are located at the periphery of the lobule. Plates of hepatic cells radiate centrifugally from the central vein like spokes on a wheel (Fig. 28-3). These hepatic plates are separated by wide, thin-walled channels, called *sinusoids*, that extend from the periphery of the lobule to its central vein. The sinusoids are



■ **FIGURE 28-2** ■ The portal circulation. Blood from the gastrointestinal tract, spleen, and pancreas travels to the liver by way of the portal vein before moving into the vena cava for return to the heart.



■ **FIGURE 28-3** ■ A section of liver lobule showing the location of the hepatic veins, hepatic cells, liver sinusoids, and branches of the portal vein and hepatic artery.

supplied by blood from the portal vein and hepatic artery. Because the plates of hepatic cells are no more than two layers thick, every cell is exposed to the blood that travels through the sinusoids. Thus, the hepatic cells can remove substances from the blood or can release substances into the blood as it moves through the sinusoids.

The venous sinusoids are lined with two types of cells: endothelial cells and Kupffer's cells. *Kupffer's cells* are phagocytic cells that are capable of removing old and defective blood cells, bacteria, and other foreign material from the portal blood as it flows through the sinusoid. This phagocytic action removes the enteric bacilli and other harmful substances that filter into the blood from the intestine.

The lobules also are supplied by small tubular channels, called *bile canaliculi*, that lie between the cell membranes of adjacent hepatocytes. The bile produced by the hepatocytes flows into the canaliculi and then to the periphery of the lobules, which drain into progressively larger ducts, until it reaches the right and left hepatic ducts. The intrahepatic and extrahepatic bile ducts often are collectively referred to as the *hepatobiliary tree*. These ducts unite to form the common duct (see Fig. 28-1). The common duct, which is approximately 10 to 15 cm long, descends and passes behind the pancreas and enters the descending duodenum. The pancreatic duct joins the common duct at a short dilated tube called the *hepatopancreatic ampulla* (ampulla of Vater), which empties into the duodenum through the duodenal papilla. Muscle tissue at the junction of the papilla, called the *sphincter of the bile duct*, regulates the flow of bile into the duodenum. When this sphincter is closed, bile moves back into the common duct and gallbladder.

Metabolic Functions of the Liver

The liver is one of the most versatile and active organs in the body. It produces bile; metabolizes hormones and drugs; synthesizes proteins, glucose, and clotting factors; stores vitamins and minerals; changes ammonia produced by deamination of amino acids to urea; and converts fatty acids to ketones. In its capacity for metabolizing drugs and hormones, the liver serves as an excretory organ. In this respect, the bile, which carries the end-products of substances metabolized by the liver, is much like the urine, which carries the body wastes filtered by the kidneys.

Carbohydrate, Protein, and Lipid Metabolism

The liver plays an essential role in carbohydrate, fat, and proteins metabolism. It degrades excess nutrients and converts them into substances essential to the body. It builds carbohydrates from proteins, converts sugars to fats that can be stored, and interchanges chemical groups on amino acids so that they can be used for a number of purposes.

Carbohydrate Metabolism. The liver is especially important in maintaining glucose homeostasis. It stores excess glucose as glycogen and releases it into the circulation when blood glucose levels fall. The liver converts galactose and fructose to glucose and it synthesizes glucose from amino acids, glycerol, and lactic acid as a means of maintaining blood glucose during periods of fasting or increased need. The liver also converts excess carbohydrates to triglycerides for storage in adipose tissue.

Protein Synthesis and Conversion of Ammonia to Urea. Even though the muscle contains the greatest amount of protein, the liver has the greatest rate of protein synthesis per gram of tissue. It produces the proteins for its own cellular needs and secretory proteins that are released into the circulation. The most important of these secretory proteins is albumin. Albumin contributes significantly to the plasma colloidal osmotic pressure (see Chapter 6) and to the binding and transport of numerous substances, including some hormones, fatty acids, bilirubin, and other anions. The liver also produces other important proteins, such as fibrinogen and the blood clotting factors.

Proteins are made up of amino acids. Protein synthesis and degradation involves two major reactions: transamination and deamination. In *transamination*, the amino group (NH_2) from an amino acid is transferred to α-ketoglutaric acid (a Krebs cycle keto acid) to form glutamic acid. The transferring amino acid becomes a keto acid and α-ketoglutaric acid becomes an amino acid (glutamic acid). The reaction is fully reversible. The process of transamination is catalyzed by *aminotransferases*, enzymes that are found in high amounts in the liver. Oxidative *deamination* involves the removal of an amino group from an amino acid. This occurs mainly by transamination, in which the amino group of glutamic acid is removed as ammonia, and α-ketoglutaric is regenerated. Because ammonia is very toxic to body tissues, particularly neurons, it is converted to urea in the liver and then excreted by the kidneys.[2] The goal of amino acid degradation is to produce molecules that can be used to produce energy or be converted to glucose.

Pathways of Lipid Metabolism. Although most body cells can metabolize fat, certain aspects of lipid metabolism occur mainly in the liver. These include the oxidation of fatty acids to supply energy for other body functions; the synthesis of large quantities of cholesterol, phospholipids, and most lipoproteins; and the formation of triglycerides from carbohydrates and proteins. To derive energy from neutral fats (triglycerides), the fat must first be split into glycerol and fatty acids, and then the fatty acids split into acetyl-coenzyme A (acetyl-CoA). Acetyl-CoA can be used by the liver to produce adenosine triphosphate (ATP) or it can be converted to acetoacetic acid and released into the bloodstream and transported to other tissues, where it is used for energy. The acetyl-CoA units from fat metabolism also are used to synthesize cholesterol and bile acids. Cholesterol has several fates in the liver. It can be esterified and stored; it can be exported bound to lipoproteins; or it can be converted to bile acids.

KEY CONCEPTS

DISEASES OF THE LIVER

- Diseases of the liver can affect the hepatocytes or the biliary drainage system.
- Disorders of hepatocyte function impair the metabolic and synthetic functions of the liver, causing disorders in carbohydrate, protein, and fat metabolism; metabolism and removal of drugs, hormones, toxins, ammonia, and bilirubin from the blood; and the interconversion of amino acids and synthesis of proteins. Elevations in serum aminotransferase levels signal the presence of hepatocyte damage.
- Disorders of the biliary drainage system obstruct the flow of bile and interfere with the elimination of bile salts and bilirubin, producing cholestatic liver damage because of the backup of bile into the lobules of the liver. Elevations in bilirubin and alkaline phosphatase signal the presence of cholestatic liver damage.

Drug and Hormone Metabolism

By virtue of its many enzyme systems that are involved in biochemical transformations and modifications, the liver has an important role in the metabolism of many drugs and chemical substances. The liver is particularly important in terms of metabolizing lipid-soluble substances that cannot be directly excreted by the kidneys. Two major types of reactions are involved in the hepatic detoxification and metabolism of drugs and other chemicals: phase 1 reactions, which involve chemical modification or inactivation of a substance, and phase 2 reactions, which involve conversion of lipid-soluble substances to water-soluble derivatives.[3,4] Often, the two types of reactions are linked. Many phase 1 reactants are not soluble and must therefore undergo a subsequent phase 2 reaction to be eliminated. These reactions, which are called *biotransformations*, are important considerations in drug therapy. Because the liver is central to metabolic disposition of virtually all drugs and foreign substances, drug-induced liver toxicity is a potential complication of many medications.

In addition to its role in metabolism of drugs and chemicals, the liver also is responsible for hormone inactivation or modification. Insulin and glucagon are inactivated by proteolysis or deamination. Thyroxine and triiodothyronine are metabolized by reactions involving deiodination. Steroid hormones such as the glucocorticoids are first inactivated by a phase 1 reaction and then converted to a more water-soluble product by a phase 2 reaction.

Bile Production and Cholestasis

The secretion of bile, approximately 600 to 1200 mL daily, is one of the many functions of the liver.[1] Bile functions in the digestion and absorption of fats and fat-soluble vitamins from the intestine, and it serves as a vehicle for excretion of bilirubin, excess cholesterol, and metabolic end-products that cannot be eliminated in the urine.

Bile contains water, electrolytes, bile salts, bilirubin, cholesterol, and certain products of organic metabolism. Of these, only the bile salts, which are formed from cholesterol, are important in digestion. Bile salts aid in emulsifying dietary fats, and they are necessary for the formation of the micelles that transport fatty acids and fat-soluble vitamins to the surface of the intestinal mucosa for absorption. Approximately 94% of bile salts that enter the intestine are reabsorbed into the portal circulation by an active transport process that takes place in the distal ileum. From the portal circulation, the bile salts pass into the liver, where they are recycled. Normally, bile salts travel this entire circuit approximately 18 times before being

expelled in the feces.[1] This system for recirculation of bile is called the *enterohepatic circulation*.

Cholestasis

Cholestasis represents a decrease in bile flow through the intrahepatic canaliculi and a reduction in secretion of water, bilirubin, and bile acids by the hepatocytes. As a result, the materials normally transferred to the bile, including bilirubin, cholesterol, and bile acids, accumulate in the blood.[5,6] The condition may be caused by intrinsic liver disease, in which case it is referred to as *intrahepatic cholestasis*, or by obstruction of the larger bile ducts located outside the liver, a condition known as *extrahepatic cholestasis*.

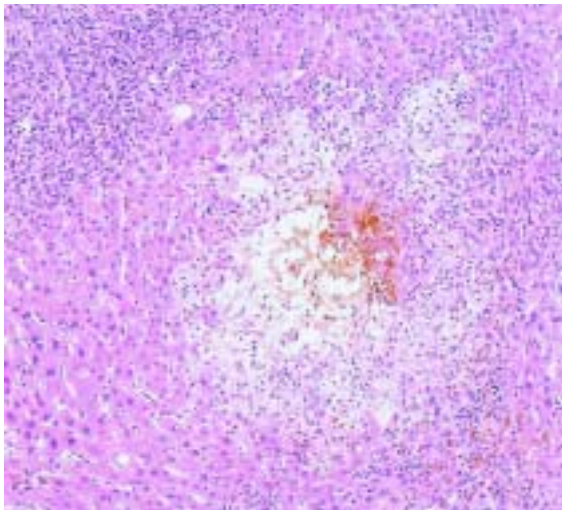
Common to all types of obstructive and hepatocellular cholestasis is the accumulation of bile pigment within the bile canaliculi and hepatocytes. Prolonged obstructive cholestasis leads not only to fatty changes in the hepatocytes but to destruction of the supporting connective tissue, giving rise to bile lakes filled with cellular debris and pigment (Fig. 28-4).[5] Unrelieved obstruction leads to portal tract fibrosis and ultimately to end-stage biliary cirrhosis.

Pruritus is the most common presenting symptom in persons with cholestasis, probably related to an elevation in plasma bile acids. Skin xanthomas (focal accumulations of cholesterol) may occur, the result of hyperlipidemia and impaired excretion of cholesterol. A characteristic laboratory finding is an elevated serum alkaline phosphatase level. Alkaline phosphatase is present in the membranes between liver cells and the bile duct and is released by disorders affecting the bile duct. Other manifestations of reduced bile flow relate to intestinal absorption, including nutritional deficiencies of the fat-soluble vitamins A, D, and K.

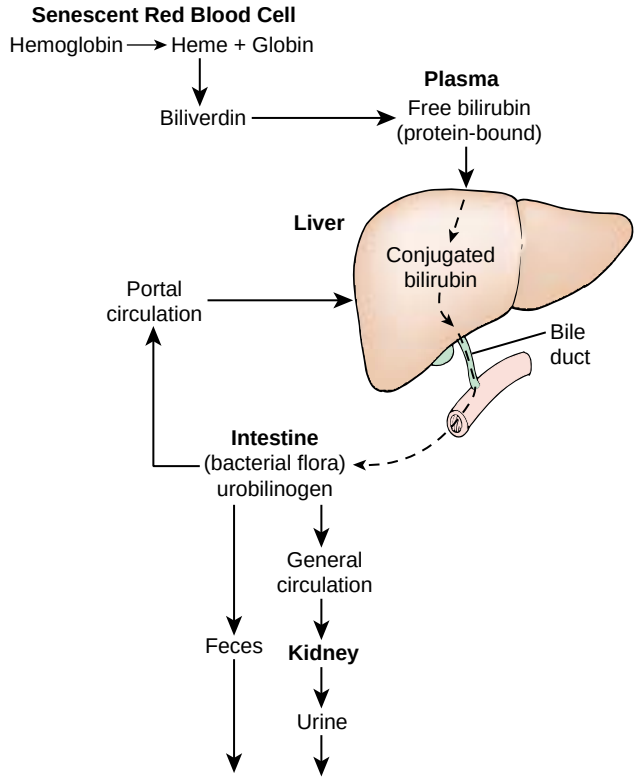
Bilirubin Elimination

Bilirubin is the substance that gives bile its color. It is formed during the breakdown of senescent red blood cells. In the process of degradation, the heme portion of the hemoglobin molecule is oxidized to form biliverdin, which is then converted to free bilirubin (Fig. 28-5). Free bilirubin, which is insoluble in plasma, is transported in the blood attached to plasma albumin. Even when it is bound to albumin, this bilirubin is still called *free bilirubin*. As it passes through the liver, free bilirubin is released from the albumin carrier molecule and moved into the hepatocytes. Inside the hepatocytes, free bilirubin is converted to conjugated bilirubin, making it soluble in bile. Conjugated bilirubin is secreted as a constituent of bile, and in this form it passes through the bile ducts into the small intestine. In the intestine, approximately one half of the bilirubin is converted into a highly soluble substance called *urobilinogen* by the intestinal flora. Urobilinogen is either absorbed into the portal circulation or excreted in the feces. Most of the urobilinogen that is absorbed is returned to the liver to be re-excreted into the bile. A small amount of urobilinogen, approximately 5%, is absorbed into the general circulation and then excreted by the kidneys.

Usually, only a small amount of bilirubin (0.1 to 1.2 mg/dL) is found in the blood. Laboratory measurements of bilirubin usually measure the free and the conjugated bilirubin as well as the total bilirubin. These are reported as the direct (conjugated) bilirubin and the indirect (unconjugated or free) bilirubin.

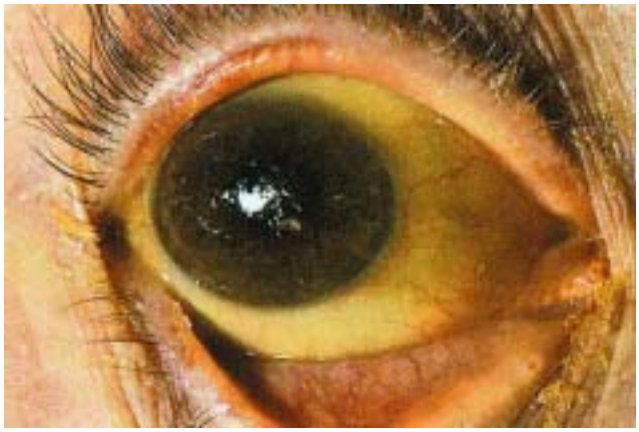


■ **FIGURE 28-4** ■ Bile infarct (bile lake). A photomicrograph of the liver in a patient with extrahepatic biliary obstruction shows an area of necrosis and the accumulation of extravasated bile (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 768]. Philadelphia: Lippincott Williams & Wilkins)



■ **FIGURE 28-5** ■ The process of bilirubin formation, circulation, and elimination.

Jaundice. Jaundice (*i.e.*, icterus), which results from an abnormally high accumulation of bilirubin in the blood, is a yellowish discoloration to the skin and deep tissues. Jaundice becomes evident when the serum bilirubin levels rise above 2.0 to 2.5 mg/dL.[5,6] Because normal skin has a yellow cast, the early signs of jaundice often are difficult to detect, especially in per-



■ **FIGURE 28-6** ■ Jaundice. A patient with hepatic failure displays a yellow sclera. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 762]. Philadelphia: Lippincott Williams & Wilkins)

sons with dark skin. Bilirubin has a special affinity for elastic tissue. The sclera of the eye, which contains considerable elastic fibers, usually is one of the first structures in which jaundice can be detected (Fig 28-6).

The four major causes of jaundice are excessive destruction of red blood cells, impaired uptake of bilirubin by the liver cells, decreased conjugation of bilirubin, and obstruction of bile flow in the canaliculi of the hepatic lobules or in the intrahepatic or extrahepatic bile ducts. From an anatomic standpoint, jaundice can be categorized as prehepatic, intrahepatic, and posthepatic. Chart 28-1 lists the common causes of prehepatic, hepatic, and posthepatic jaundice.

CHART 28-1 Causes of Jaundice

Prehepatic (Excessive Red Blood Cell Destruction)

Hemolytic blood transfusion reaction
Hereditary disorders of the red blood cell
- Sickle cell anemia
- Thalassemia
- Spherocytosis

Acquired hemolytic disorders
Hemolytic disease of the newborn
Autoimmune hemolytic anemias

Intrahepatic

Decreased bilirubin uptake by the liver
Decreased conjugation of bilirubin
Hepatocellular liver damage
- Hepatitis
- Cirrhosis
- Cancer of the liver

Drug-induced cholestasis

Posthepatic (Obstruction of Bile Flow)

Structural disorders of the bile duct
Cholelithiasis
Congenital atresia of the extrahepatic bile ducts
Bile duct obstruction caused by tumors

The major cause of prehepatic jaundice is excessive hemolysis of red blood cells. Hemolytic jaundice occurs when red blood cells are destroyed at a rate in excess of the liver's ability to remove the bilirubin from the blood. It may follow a hemolytic blood transfusion reaction or may occur in diseases such as hereditary spherocytosis, in which the red cell membranes are defective, or in hemolytic disease of the newborn (see Chapter 13). Neonatal hyperbilirubinemia results in an increased production of bilirubin in newborn infants and their limited ability to excrete it.[7] Premature infants are at particular risk because their red cells have a shorter life span and higher turnover rate. In prehepatic jaundice, there is mild jaundice, the unconjugated bilirubin is elevated, the stools are of normal color, and there is no bilirubin in the urine.

Intrahepatic or hepatocellular jaundice is caused by disorders that directly affect the ability of the liver to remove bilirubin from the blood or conjugate it so it can be eliminated in the bile. Liver diseases such as hepatitis and cirrhosis are the most common causes of intrahepatic jaundice. Intrahepatic jaundice usually interferes with all phases of bilirubin metabolism—uptake, conjugation, and excretion. Both conjugated and unconjugated bilirubin are elevated and the urine often is dark because of the presence of bilirubin.

Posthepatic or obstructive jaundice, also called *cholestatic jaundice*, occurs when bile flow is obstructed between the liver and the intestine. Among the causes of posthepatic jaundice are strictures of the bile duct, gallstones, and tumors of the bile duct or the pancreas. Conjugated bilirubin levels usually are elevated; the stools are clay colored because of the lack of bilirubin in the bile; the urine is dark; the levels of serum alkaline phosphatase are markedly elevated; and the aminotransferase levels are slightly increased. Blood levels of bile acids often are elevated in obstructive jaundice. As the bile acids accumulate in the blood, pruritus develops. A history of pruritus preceding jaundice is common in obstructive jaundice.

Tests of Hepatobiliary Function

The history and physical examination, in most instances, provide clues about liver function. Diagnostic tests help to evaluate liver function and the extent of liver damage. Laboratory tests commonly are used to assess liver function and confirm the diagnosis of liver disease.

Liver function tests, including serum levels of liver enzymes, are used to assess injury to liver cells, the liver's ability to synthesize proteins, and the excretory functions of the liver.[8,9] Elevated serum enzyme tests usually indicate liver injury earlier than do other indicators of liver function. The key enzymes are alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which are present in liver cells. ALT is liver specific, whereas AST is derived from organs other than the liver. In most cases of liver damage, there are parallel increases in ALT and AST. The most dramatic rise is seen in cases of acute hepatocellular injury, such as occurs with viral hepatitis, hypoxic or ischemic injury, and acute toxic injury.

The liver's synthetic capacity is reflected in measures of serum protein levels and prothrombin time (*i.e.*, synthesis of coagulation factors). Hypoalbuminemia caused by depressed synthesis may complicate severe liver disease. Deficiencies of coagulation factor V and vitamin K-dependent factors (II, VII, IX, and X) may occur.

Serum bilirubin, γ-glutamyltransferase (GGT), and alkaline phosphatase measure hepatic excretory function. Alkaline phosphatase is present in the membranes of cells that line the bile duct and is released by disorders affecting the bile duct.[8] GGT is thought to function in the transport of amino acids and peptides into liver cells; it is a sensitive indicator of hepatobiliary disease. Measurement of GGT may be helpful in diagnosing alcohol abuse.[9]

Ultrasonography and computed tomography (CT) scanning provide information about the size, structure, and composition of the liver. Magnetic resonance imaging (MRI) has proved to be useful in some disorders. Selective angiography of the celiac, superior mesenteric, or hepatic artery may be used to visualize the hepatic or portal circulation. A liver biopsy affords a means of examining liver tissue without surgery.

In summary, the hepatobiliary system consists of the liver, gallbladder, and bile ducts. The liver is the largest and, in functions, one of the most versatile organs in the body. It is located between the gastrointestinal tract and the systemic circulation; venous blood from the intestine flows through the liver before it is returned to the heart. In this way, nutrients can be removed for processing and storage, and bacteria and other foreign matter can be removed by Kupffer's cells before the blood is returned to the systemic circulation.

The liver synthesizes fats, glucose, and plasma proteins. Other important functions of the liver include the deamination of amino acids, conversion of ammonia to urea, and the interconversion of amino acids and other compounds that are important to the metabolic processes of the body. The liver produces approximately 600 to 1200 mL of bile daily. Bile contains bile salts that are essential for digestion of fats and absorption of fat-soluble vitamins, and it serves as an excretory vehicle for bilirubin, cholesterol, and certain products of organic metabolism. Cholestasis represents a decrease in bile flow through the intrahepatic bile ducts. It results in destructive liver changes and an accumulation of bile components in the blood. The liver also removes, conjugates, and secretes bilirubin into the bile. Jaundice occurs when bilirubin accumulates in the blood. It can occur because of excessive red blood cell destruction, failure of the liver to remove and conjugate the bilirubin, or obstructed biliary flow.

Liver function tests, including serum aminotransferase levels, are used to assess injury to liver cells. Serum bilirubin, GGT, and alkaline phosphatase measure hepatic excretory function. Ultrasonography, CT scans, and MRI are used to evaluate liver structures. Angiography may be used to visualize the hepatic or portal circulation, and a liver biopsy may be used to obtain tissue specimens for microscopic examination.

DISORDERS OF THE LIVER

The liver is subject to many of the same pathologic conditions that affect other body organs: infection, inflammation, and immune responses; metabolic disorders; and neoplasms. This section focuses on alterations in liver function caused by viral and autoimmune hepatitis; intrahepatic biliary tract disorders; alcohol-induced liver disease; cirrhosis, portal hypertension, and liver failure; and cancer of the liver.

Hepatitis

Hepatitis refers to inflammation of the liver. It can be caused by reactions to chemical agents, drugs, and toxins; disorders such as autoimmune diseases and infectious mononucleosis that cause secondary hepatitis; and by hepatotropic viruses that primarily affect liver cells or hepatocytes.

Acute Viral Hepatitis

The known hepatotropic viruses include hepatitis A virus (HAV), hepatitis B virus (HBV), the hepatitis B-associated delta virus (HDV), hepatitis C virus (HCV), and hepatitis E virus (HEV). Although all of these viruses cause acute hepatitis, they differ in the mode of transmission and incubation period; mechanism, degree, and chronicity of liver damage; and ability to evolve to a carrier state.

There are two mechanisms of liver injury in viral hepatitis: direct cellular injury and immune responses against viral antigens in infected hepatocytes. The immune-mediated mechanisms of injury have been most closely studied in HBV. It is thought that the extent of inflammation and necrosis depends on the person's immune response. Accordingly, a prompt immune response during the acute phase of the infection would be expected to cause cell injury but at the same time eliminate the virus. Thus, people who respond with fewer symptoms and a marginal immune response are less likely to eliminate the virus, and hepatocytes expressing the viral antigens persist, leading to the chronic or carrier state. Fulminant hepatitis would be explained in terms of an accelerated immune response with severe liver necrosis.

The clinical course of viral hepatitis involves a number of syndromes, including asymptomatic infection with only serologic evidence of disease; acute symptomatic hepatitis; the carrier state without clinically apparent disease or with chronic hepatitis; chronic hepatitis with or without progression to cirrhosis; or fulminating disease (>1% to 3%) with rapid onset of liver failure. Not all hepatotropic viruses provoke each of the clinical syndromes.

The manifestations of acute hepatitis can be divided into three phases: the prodromal or preicterus period, the icterus period, and the convalescent period. The *prodromal period* is marked by nonspecific symptoms, which vary from abrupt to insidious. There are usually complaints of malaise, easy fatigability, nausea, and loss of appetite. Weight loss, low-grade fever, headaches, muscle aches and pains, vomiting, and diarrhea are less constant symptoms. In some persons, the nonspecific symptoms are more severe with higher fever, chills, and headache, sometimes accompanied by right upper quadrant abdominal pain and liver enlargement and tenderness. Serum levels of AST and ALT show variable increases during the preicterus phase and precede a rise in serum bilirubin that accompanies the onset of the icterus or jaundice phase of infection. The *icterus* or *jaundice phase*, if it occurs, usually follows the prodromal phase by 5 to 10 days. Jaundice is less likely to occur with HCV infection. The symptoms may become worse with the onset of jaundice, followed by progressive clinical improvement. Severe pruritus and liver tenderness are common during

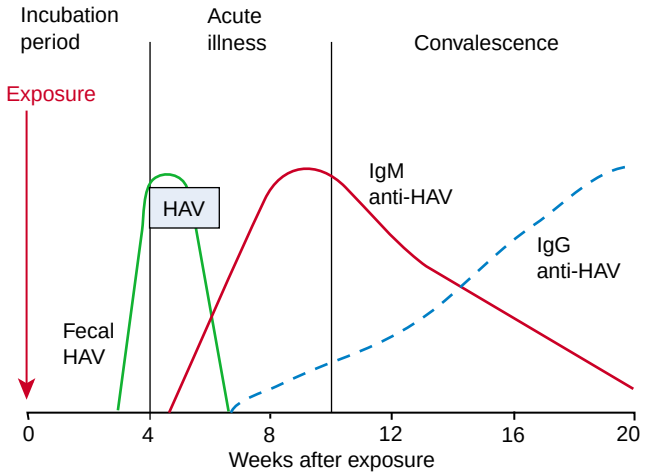
the icterus period. The *convalescent phase* is characterized by an increased sense of well-being, return of appetite, and disappearance of jaundice. The acute illness usually subsides gradually during a 2- to 3-week period, with complete clinical recovery by approximately 9 weeks in hepatitis A and 16 weeks in uncomplicated hepatitis B.

Infection with HBV and HCV can produce a *carrier state*, in which the person does not have symptoms but harbors the virus and can transmit the disease. Evidence also indicates a carrier state for HDV infection. There is no carrier state for HAV infection. There are two types of carriers: healthy carriers who have few or no ill effects, and those with chronic disease who may or may not have symptoms. Factors that increase the risk of becoming a carrier are age at time of infection and immune status. Persons at high risk for becoming carriers are infants of HBV-infected mothers, persons with impaired immunity, those who have received multiple transfusions or blood products, those who are on hemodialysis, and drug addicts.

Hepatitis A. Hepatitis A, formerly called *infectious hepatitis*, is caused by the small, unenveloped, RNA-containing HAV. It usually is a benign, self-limited disease, although in rare cases it can cause acute fulminant hepatitis and liver failure, leading to death. The onset of symptoms usually is abrupt and includes fever, malaise, nausea, anorexia, abdominal discomfort, dark urine, and jaundice. The likelihood of having symptoms is related to age.[10] Children younger than 6 years often are asymptomatic. The illness in older children and adults usually is symptomatic, and jaundice occurs in approximately 90% of cases. Symptoms usually last approximately 2 months but can last longer. HAV does not cause chronic hepatitis or induce a carrier state.

Hepatitis A has a brief incubation period (15 to 45 days) and usually is transmitted by the fecal-oral route.[5,6,11] The virus replicates in the liver, is excreted in the bile, and shed in the stool. The fecal shedding of HAV occurs as much as 2 weeks before the development of symptoms and ends as the immunoglobulin M (IgM) levels rise.[5] The disease often occurs sporadically or in epidemics. Drinking contaminated milk or water and eating shellfish from infected waters are fairly common routes of transmission. At special risk are persons traveling abroad who have not previously been exposed to the virus. Because young children are asymptomatic, they play an important role in the spread of the disease. Institutions housing large numbers of persons (usually children) sometimes are stricken with an epidemic of hepatitis A. Oral behavior and lack of toilet training promote viral infection among children attending preschool day care centers, who then carry the virus home to older siblings and parents. Hepatitis A usually is not transmitted by transfusion of blood or plasma derivatives, presumably because its short period of viremia usually coincides with clinical illness, so that the disease is apparent and blood donations are not accepted.

Antibodies to HAV (anti-HAV) appear early in the disease and tend to persist in the serum (Fig. 28-7). The IgM antibodies (see Chapter 8) usually appear during the first week of symptomatic disease and begin to decline in a few months. Their presence coincides with a decline in fecal shedding of the virus. Peak levels of IgG antibodies occur after 1 month of illness and may persist for years; they provide long-term protective immunity against reinfection. The presence of IgM anti-HAV is indicative of acute hepatitis A, whereas IgG anti-HAV merely documents past exposure.



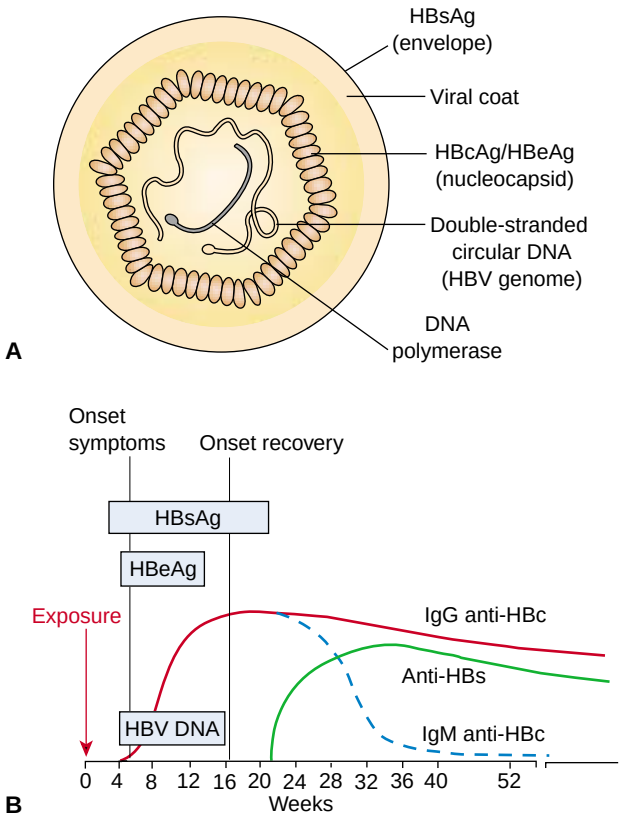
■ **FIGURE 28-7** ■ The sequence of fecal shedding of the hepatitis A virus (HAV), HAV viremia, and HAV antibody (IgM and IgG anti-HAV) changes in hepatitis A.

Two commercially prepared hepatitis A vaccines are available; vaccination is recommended for persons at risk for HAV exposure. It is recommended for international travelers to regions where sanitation is poor and endemic HAV infections are high, children living in communities with high rates of HAV infection, homosexually active men, and users of illicit drugs.[10] A public health benefit also may be derived from vaccinating persons with increased potential for transmitting the disease (*e.g.*, food handlers). An immune globulin is available for persons with known HAV exposure who have not been immunized.

Hepatitis B. The Centers for Disease Control (CDC) estimates that there are 200,000 to 300,000 new cases of hepatitis B each year and 1 to 1.25 million chronic carriers in the United States.[12] The CDC also estimates that each year in the United States there are 4000 to 5000 deaths associated with hepatitis B-related cirrhosis and hepatocellular carcinoma. These figures are dwarfed by a much higher frequency of hepatitis B on a global scale. For example, the infection is endemic in regions of Africa and Southeast Asia.

Hepatitis B is caused by a double-stranded DNA virus (HBV).[5,6,13,14] The complete virion, also called a *Dane particle*, consists of an outer envelope and an inner core that contains HBV DNA and DNA polymerase (Fig. 28-8). Hepatitis B has a longer incubation period and represents a more serious health problem than does hepatitis A. It can produce acute hepatitis, chronic hepatitis, progression of chronic hepatitis to cirrhosis, fulminant hepatitis with massive hepatic necrosis, and the carrier state. It also participates in the development of hepatitis D (delta hepatitis).

The HBV usually is transmitted through inoculation with infected blood or serum. However, the viral antigen can be found in most body secretions and can be spread by oral or sexual contact. In the United States, most persons with hepatitis B acquire the infection as adults or adolescents. The disease is highly prevalent among injecting drug users, persons with multiple sex



■ **FIGURE 28-8** ■ (**A**) The hepatitis B virus. (**B**) The sequence of hepatitis B virus (HBV) viral antigens (HBsAg, HBeAg), HBV DNA, and HBV antibody (IgM, IgG, anti-HBc, and anti-HBs) changes in acute resolving hepatitis B.

partners, and men who have sex with men.[15] Health care workers are at risk because of blood exposure and accidental needle injuries. Although the virus can be spread through transfusion or administration of blood products, routine screening methods have appreciably reduced transmission through this route. The risk that infants born to infected mothers will have hepatitis B ranges from 10% to 85%, depending on the mother's HBV core antigen (HBeAg) status. Infants who become infected have a 90% risk of becoming chronic carriers, and as many as 25% will die of chronic liver disease as adults.[12]

Three well-defined antigens are associated with the virus: two nucleocapsid "core" antigens, HBcAg and HBeAg, and a third, HbsAg, surface antigen (see Fig. 28-8). These HBV antigens evoke specific antibodies: anti-HBs, anti-HBc, and anti-HBe. These antigens and their antibodies serve as serologic markers for following the course of the disease.

The *HBsAg* is the viral antigen measured most routinely in blood. It is produced in abundance by infected liver cells and released into the serum. HBsAg is the earliest serologic marker to appear; it appears before the onset of symptoms and is an indicator of acute or chronic infection. The HBsAg level begins to decline after the onset of the illness and usually is undetectable in 3 to 6 months. Persistence beyond 6 months indicates continued viral replication, infectivity, and the risk of chronic hepatitis. *Anti-HBs*, a specific antibody to HBsAg, occurs in most individuals after clearance of HBsAg and after successful immunization for hepatitis B. There often is a delay in appearance of anti-HBs after clearance of HBsAg. During this period of serologic gap, called the *window period*, infectivity has been demonstrated. Development of anti-HBs signals recovery from HBV infection, noninfectivity, and protection from future HBV infection.

The *HBeAg* is thought to be a cleavage product of the viral core antigen; it may be found in the serum and is an active marker for the disease and shedding of complete virions into the bloodstream. It appears during the incubation period, shortly after the appearance of HBsAg, and is found only in the presence of HBsAg. HBeAg usually disappears before HBsAg. The antibody to HBeAg, *anti-HBe*, begins to appear in the serum at about the time that HBeAg disappears, and its appearance signals the onset of resolution of the acute illness. The clinical usefulness of the antigen and its antibody lies in their predictive value as markers for infectivity.

The *HBcAg* does not circulate in the blood; therefore, it is not a useful marker for the disease. Although the antigen is not found in the blood, its antibodies (anti-HBc) are the first to be detected. They appear toward the end of the incubation period and persist during the acute illness and for several months to years after that. The initial HBcAg antibody is IgM; it serves as a marker for recent infection and is followed in 6 to 18 months by IgG antibodies. These antibodies are not protective and are detectable in the presence of chronic disease.

The presence of viral DNA (HBV DNA) in the serum is the most certain indicator of hepatitis B infection. It is transiently present during the presymptomatic period and for a brief time during the acute illness. The presence of DNA polymerase, the enzyme used in viral replication, usually is transient but may persist for years in persons who are chronic carriers and is an indication of continued infectivity.

Hepatitis B vaccine provides long-term protection against HBV infection.[16] Vaccination is recommended for all children ages 0 to 18 years as a means of preventing HBV transmission.[15] The vaccine also is recommended for all persons who are at high risk for exposure to the virus. All pregnant women should be tested for HBsAg during an early prenatal visit, and infants born to HBsAg-positive mothers should receive appropriate doses of hepatitis immune globulin and hepatitis B vaccine.[12]

Hepatitis C. Hepatitis C is caused by a single-stranded RNA virus (HCV) that is distantly related to the viruses that cause yellow fever and dengue fever. There are at least six genotypes of the hepatitis C virus and multiple subtypes of the virus.[17] It is likely that the wide diversity of genotypes contributes to the pathogenicity of the virus, allowing it to escape the actions of host immune mechanisms and antiviral medications, and to the difficulties in developing a preventative vaccine.[18,19]

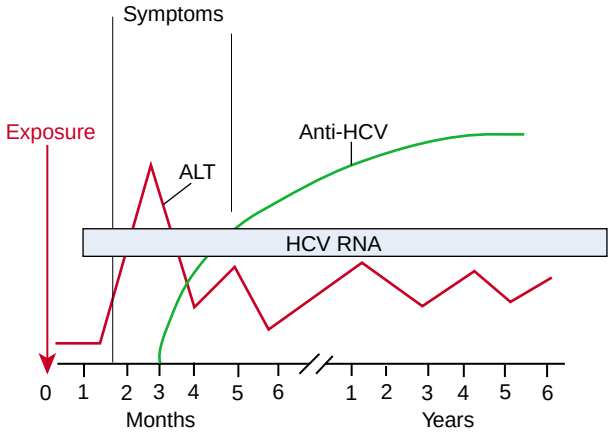
Hepatitis C is the most common cause of chronic hepatitis, cirrhosis, and hepatocellular cancer in the world.[17,18] An estimated 2.7 million people in the United States have active HCV infection.[17] Most of these people are chronically infected and unaware of their infection because they are not clinically ill. Infected persons serve as a source of infection to others and are at risk for chronic liver disease during the first two or more decades after initial infection.

Before 1990, the main route of transmission was through contaminated blood transfusions or blood products. With implementation of HCV testing in blood banks, the risk of HCV infection from blood transfusion is less than 1 in 103,000.[14]

Currently, injecting drug use is thought to be the single most important risk factor for HCV infection. There also is concern that transmission of small amounts of blood during tattooing, acupuncture, and body piercing may facilitate the transmission of HCV.[19] The incidence of sexual and vertical transmission from mother to child is uncertain. Occupational exposure through incidents such as unintentional needle sticks can result in infection. However, the prevalence of HCV among health care, emergency medical, and public safety workers who are exposed to blood in the workplace is reported to be no greater than in the general public.[17,18] Sporadic cases of hepatitis C of unknown source account for approximately 40% of cases.

The incubation period for HCV infection ranges from 15 to 150 days (average, 50 days). Clinical symptoms with acute hepatitis C tend to be milder than those seen in persons with other types of viral hepatitis. Children and adults who acquire the infection usually are asymptomatic, or have a nonspecific clinical disease characterized by fatigue, malaise, anorexia, and weight loss. Jaundice is uncommon, and only 25% to 30% of symptomatic adults have jaundice.[20] Unlike hepatitis A and B viral infections, fulminant hepatic failure is rare, and only a few cases have been reported. The most alarming aspects of HCV infection are its high rate of persistence and ability to induce chronic hepatitis and cirrhosis. HCV also increases the risk for development of hepatocellular cancer.

Both antibody and viral tests are available for detecting the presence of hepatitis C infection (Fig 28-9). Antibody testing has the advantage of being readily available and having a relatively low cost. False-negative results can occur in immunocompromised people and early in the course of the disease before antibodies develop. Direct measurement of HCV in the serum remains the most accurate test for infection. The viral tests are highly sensitive and specific but more costly than antibody tests. With newer antibody testing methods, infection often can be detected as early as 6 to 8 weeks after exposure, and as early as 1 to 2 weeks with viral tests that use the polymerase chain reaction (PCR) testing methods. Unlike hepatitis A and B, antibodies to HCV are not protective, but they serve as markers for the disease. At present, there is no vaccine that protects against HCV infection.



■ **FIGURE 28-9** ■ The sequence of serologic changes in chronic hepatitis C with persistence of hepatitis C virus (HCV) RNA and exacerbations and remissions of clinical symptoms designated by changes in serum alanine aminotransferase (ALT) levels.

Hepatitis D. Also called the *hepatitis delta virus*, HDV is a defective RNA virus that can cause acute or chronic hepatitis. Infection depends on concomitant infection with hepatitis B, specifically the presence of HBsAg. Acute hepatitis D occurs in two forms: coinfection that occurs simultaneously with acute hepatitis B, and as a super-infection in which hepatitis D is imposed on chronic hepatitis B or hepatitis B carrier state.[21] The HDV often increases the severity of HBV infection. It can convert mild HBV infection into severe, fulminating hepatitis, cause acute hepatitis in asymptomatic carriers, or increase the tendency for progression to chronic hepatitis and cirrhosis.

The routes of transmission of HDV are similar to those for HBV. In the United States, infection is restricted largely to persons at high risk for HBV infection, particularly injecting drug users and persons receiving clotting factor concentrates. The greatest risk is in HBV carriers; these persons should be informed about the dangers of HDV superinfection. Hepatitis D is diagnosed by detection of antibody to HDV (anti-HDV) in the serum or HDV RNA in the serum. There is no specific treatment for hepatitis D. Because the infection is linked to hepatitis B, prevention of hepatitis D should begin with prevention of hepatitis B through vaccination.

Hepatitis E. The hepatitis E virus is an unenveloped, single-stranded RNA virus. It is transmitted by the fecal-oral route and causes manifestations of acute hepatitis that are similar to hepatitis A. It does not cause chronic hepatitis or the carrier state. Its distinguishing feature is the high mortality rate (approximately 20%) among pregnant women attributable to the development of fulminant hepatitis. The infection occurs primarily in developing areas, such as India, other Southeast Asian countries, parts of Africa, and Mexico. The only reported cases in the United States have been in persons who have recently been in an endemic area.

Chronic Hepatitis

Chronic hepatitis is defined as inflammatory reaction of the liver of more than 3 to 6 months' duration. It is characterized by persistently elevated serum aminotransferase levels and characteristic histologic findings on liver biopsy. The causes of chronic hepatitis include HBV, HCV, HDV, autoimmune hepatitis, and hepatitis associated with certain medications.[22]

Chronic Viral Hepatitis. Chronic viral hepatitis is the principal cause of chronic liver disease, cirrhosis, and hepatocellular cancer in the world and now ranks as the chief reason for liver transplantation in adults.[23]

The clinical features of chronic viral hepatitis are highly variable and not predictive of outcome. The most common symptoms are fatigue, malaise, loss of appetite, and occasional bouts of jaundice. Elevation of serum aminotransferase levels depends on the degree of disease activity.

Chronic hepatitis B accounts for 5% to 10% of chronic liver disease and cirrhosis in the United States.[23] Hepatitis B is less likely than hepatitis C to progress to chronic infection. Chronic hepatitis B is characterized by the persistence of HBV DNA and usually by HBeAg in the serum, indicating active viral replication. Many persons are asymptomatic at the time of diagnosis, and elevated serum aminotransferase levels are the first sign of infection. Chronic hepatitis D depends on concurrent infection with HBV.

Chronic hepatitis C accounts for most cases of chronic viral hepatitis. HCV infection becomes chronic in 75% to 80% of cases.[18] Chronic HCV infection often smolders during a period of years, silently destroying liver cells. Most persons with chronic hepatitis C are asymptomatic, and diagnosis usually follows a finding of elevated serum aminotransferase levels, a tender liver, or complaints of fatigue or nonspecific weakness. Because the course of acute hepatitis C often is mild, many persons do not recall the events of the acute infection.

There are no simple and effective treatment methods for chronic viral hepatitis.[23,24] Persons with chronic hepatitis B who have evidence of active viral replication may be treated with a course of recombinant interferon α-2b. The antiviral drug lamivudine may be used as a substitute for interferon α.[23] Liver transplantation is a treatment option for end-stage liver disease caused by viral hepatitis. Liver transplantation has been more successful in persons with hepatitis C than in those with hepatitis B. Although the graft often is reinfected, the disease seems to progress more slowly.

Autoimmune Hepatitis. Chronic autoimmune hepatitis is a chronic inflammatory liver disease of unknown origin, but it is associated with circulating autoantibodies and high serum gamma globulin levels. Autoimmune hepatitis accounts for only approximately 10% of chronic hepatitis cases in the United States, a decrease from previously reported rates that probably reflects not a true change in incidence but better methods of detecting viral pathogens. The pathogenesis of the disorder is one of a genetically predisposed person exposed to an environmental agent that triggers an autoimmune response directed at liver cell antigens.[25] The resulting immune response produces a necrotizing inflammatory response that eventually leads to destruction of liver cells and development of cirrhosis. The factors surrounding the genetic predisposition and the triggering events that lead to the autoimmune response are unclear. Autoimmune hepatitis is mainly a disease of young women, although it can occur at any age and in men or women.

Clinical manifestations of the disorder cover a spectrum that extends from no apparent symptoms to the signs accompanying liver failure. In asymptomatic cases, the disorder may be discovered when abnormal serum enzyme levels are discovered during performance of routine screening tests.

The differential diagnosis includes measures to exclude other causes of liver disease, including hepatitis B and C. A characteristic laboratory finding is that of a marked elevation in serum gamma globulins. A biopsy is used to confirm the diagnosis. Corticosteroid drugs and immunosuppressant drugs are the treatment of choice for this type of hepatitis. Liver transplantation may be the only treatment for end-stage disease.

Intrahepatic Biliary Disorders

Intrahepatic biliary diseases disrupt the flow of bile through the liver, causing cholestasis and biliary cirrhosis. Among the causes of intrahepatic biliary disease are primary biliary cirrhosis, primary sclerosing cholangitis, and secondary biliary cirrhosis.

Primary Biliary Cirrhosis

Primary biliary cirrhosis involves inflammation and scarring of small intrahepatic bile ducts, portal inflammation, and progressive scarring of liver tissue.[26] The disease is seen most commonly in women 30 to 65 years of age and accounts for 2% to 5% of cases of cirrhosis. Familial occurrences of the disease are found between parents and children and among siblings. Abnormalities of cell-mediated and humoral immunity suggest an autoimmune mechanism. Antimitochondrial antibodies are found in 98% of persons with the disease, but their role in the pathogenesis of the disease is unclear.[26,27] As many as 84% of persons with primary biliary cirrhosis have at least one other autoimmune disorder, such as scleroderma, Hashimoto's thyroiditis, rheumatoid arthritis, or the sicca complex of dry eyes and mouth (Sjögren's syndrome).

The disorder is characterized by an insidious onset and progressive scarring and destruction of liver tissue. The liver becomes enlarged and takes on a green hue because of the accumulated bile. The earliest symptoms are unexplained pruritus or itching, weight loss, and fatigue, followed by dark urine and pale stools. Jaundice is a late manifestation of the disorder, as are other signs of liver failure. Serum alkaline phosphatase levels are elevated in persons with primary biliary cirrhosis.

Treatment is largely symptomatic. Liver transplantation remains the only treatment for advanced disease.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is a chronic cholestatic disease of unknown origin that causes destruction and fibrosis of intrahepatic and extrahepatic bile ducts.[28] Bile flow is obstructed (*i.e.*, cholestasis), and the bile retention destroys hepatic structures. The disease commonly is associated with inflammatory bowel disease, occurs more often in men than women, and is seen most commonly in the third to fifth decades of life. Primary sclerosing cholangitis, although much less common than alcoholic cirrhosis, is the fourth leading indication for liver transplantation in adults in the United States.[28]

Most persons with the disorder are initially asymptomatic, with the disorder being detected during routine liver function tests that reveal elevated levels of serum alkaline phosphatase or GGT. Alternatively, some persons may present with progressive fatigue, jaundice, and pruritus. The later stages of the disease are characterized by cirrhosis, portal hypertension, and liver failure. Ten-year survival rates range from 50% to 75%.[28] Other than measures aimed at symptom relief, the only treatment is liver transplantation.

Secondary Biliary Cirrhosis

Secondary biliary cirrhosis results from prolonged obstruction of the extrabiliary tree. The most common cause is cholelithiasis. Other causes of secondary biliary cirrhosis are malignant neoplasms of the biliary tree or head of the pancreas and strictures of the common duct caused by previous surgical procedures. Extrahepatic biliary cirrhosis may benefit from surgical procedures designed to relieve the obstruction.

Alcohol-Induced Liver Disease

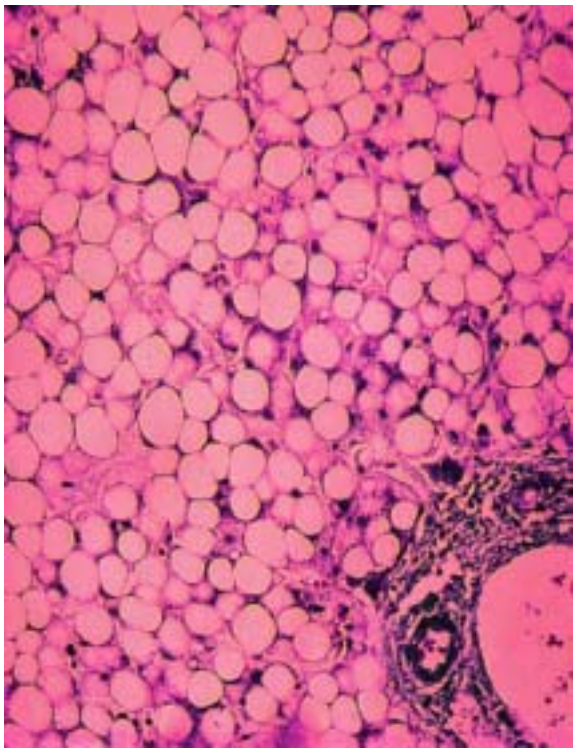
The spectrum of alcoholic liver disease includes fatty liver disease, alcoholic hepatitis, and cirrhosis. Alcoholic cirrhosis causes 200,000 deaths annually and is the fifth leading cause of death in the United States.[5] Most deaths associated with alcoholic cirrhosis are attributable to liver failure, bleeding esophageal varices, or kidney failure. It has been estimated that there are 10 million alcoholics in the United States. However,

only approximately 10% to 15% of alcoholics have cirrhosis, suggesting that other conditions such as genetic and environmental factors contribute to its occurrence.

Although the mechanism by which alcohol exerts its toxic effects on liver structures is somewhat uncertain, the changes that develop can be divided into three stages: fatty changes, alcoholic hepatitis, and cirrhosis.[5,6] *Alcoholic cirrhosis* is the end result of repeated bouts of drinking-related liver injury and designates the onset of end-stage alcoholic liver disease.

Fatty liver is characterized by the accumulation of fat in hepatocytes, a condition called *steatosis* (Fig. 28-10). The liver becomes yellow and enlarged because of excessive fat accumulation. The pathogenesis of fatty liver is not completely understood and can depend on the amount of alcohol consumed, dietary fat content, body stores of fat, hormonal status, and other factors. There is evidence that ingestion of large amounts of alcohol can cause fatty liver changes even with an adequate diet. For example, young, nonalcoholic volunteers had fatty liver changes after 2 days of consuming 18 to 24 oz of alcohol, even though adequate carbohydrates, fats, and proteins were included in the diet.[29] The fatty changes that occur with ingestion of alcohol usually do not produce symptoms and are reversible after the alcohol intake has been discontinued.

Alcoholic hepatitis is the intermediate stage between fatty changes and cirrhosis. It often is seen after an abrupt increase in alcohol intake and is common in "spree" drinkers. Alcoholic hepatitis is characterized by inflammation and necrosis of liver cells. This stage usually is characterized by hepatic tenderness, pain, anorexia, nausea, fever, jaundice, ascites, and liver failure, but some individuals may be asymptomatic. The condition is always serious and sometimes fatal. The immediate prognosis correlates with the severity of liver cell injury. In some cases, the disease progresses rapidly to liver failure and death. The mortality rate in the acute stage ranges from 10% to 30%.[6] In persons who survive and continue to drink, the acute phase often is followed by persistent alcoholic hepatitis, with progression to cirrhosis in a matter of 1 to 2 years.[6]



■ **FIGURE 28-10** ■ Alcoholic fatty liver. A photomicrograph shows the cytoplasm of almost all the hepatocytes to be distended by fat, which displaces the nucleus to the periphery. Note the absence of inflammation and fibrosis. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 791]. Philadelphia: Lippincott Williams & Wilkins)

Cirrhosis, Portal Hypertension, and Liver Failure

Cirrhosis

Cirrhosis represents the end stage of chronic liver disease in which the normal architecture of the liver is replaced by fibrous septa that encompass regenerative nodules of hepatic tissue.[5,6] The gross appearance of the liver in early alcoholic cirrhosis is one of fine, uniform nodules on its surface. The condition has traditionally been called *micronodular* or *Laennec cirrhosis*. Although the initial nodules that develop are similar in size to the lobules in normal liver tissue, they lack all the landmarks of normal lobular architecture in terms of portal tracts and central venules. With more advanced cirrhosis, regenerative processes cause the nodules to become larger and more irregular in size and shape. The nodules may compress the hepatic veins and bile ducts, producing portal hypertension, extrahepatic portosystemic shunts, and cholestasis.

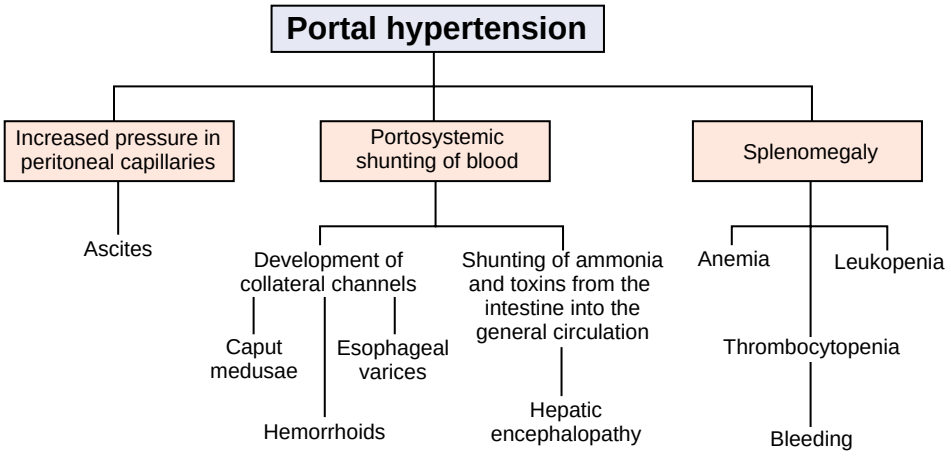
Although cirrhosis usually is associated with alcoholism, it can develop in the course of other disorders, including viral hepatitis, toxic reactions to drugs and chemicals, and biliary obstruction. Cirrhosis also accompanies metabolic disorders that cause the deposition of minerals in the liver. Two of these disorders are hemochromatosis (*i.e.*, iron deposition) and Wilson's disease (*i.e.*, copper deposition).

The manifestations of cirrhosis are variable, ranging from asymptomatic hepatomegaly to hepatic failure. Often there are no symptoms until the disease is far advanced. The most common signs and symptoms of cirrhosis are weight loss (sometimes masked by ascites), weakness, and anorexia. Diarrhea frequently is present, although some persons may report constipation. Hepatomegaly and jaundice also are common signs of cirrhosis. There may be abdominal pain because of liver enlargement or stretching of Glisson's capsule.

The late manifestations of cirrhosis are related to portal hypertension and liver failure (Fig. 28-11, Fig. 28-12). Splenomegaly, ascites, and portosystemic shunts (*i.e.*, esophageal varices, anorectal varices, and caput medusae) result from portal hypertension. Other complications include bleeding caused by decreased clotting factors; thrombocytopenia caused by splenomegaly; gynecomastia, a feminizing pattern of pubic hair distribution, and testicular atrophy in men because of altered testosterone and estrogen metabolism; spider angiomas and palmar erythema; and encephalopathy with asterixis and neurologic signs.

Portal Hypertension

Portal hypertension is characterized by increased resistance to flow in the portal venous system and sustained portal vein pressure above 12 mm Hg (normal, 5–10 mm Hg).[6,30] Normally,

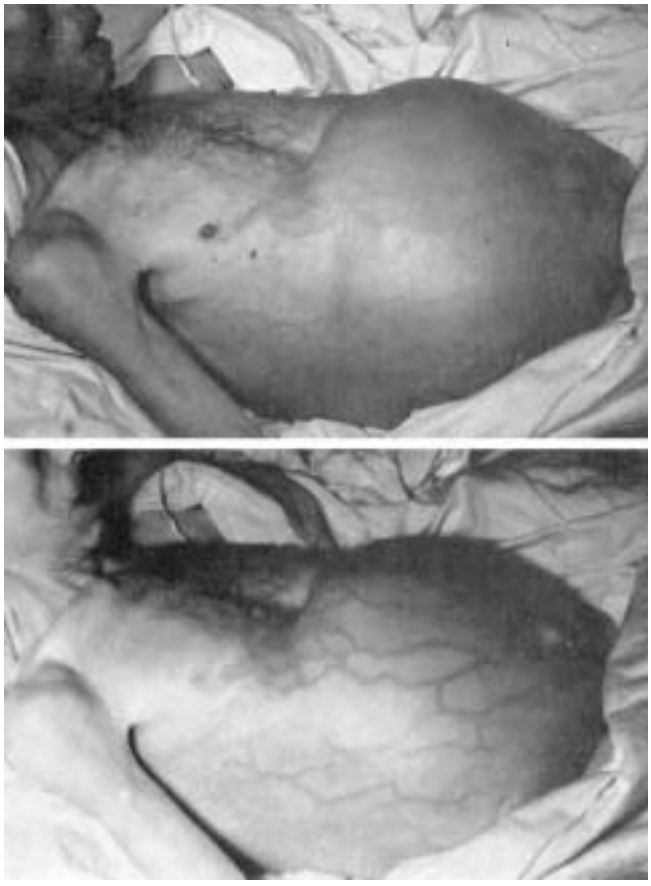


■ **FIGURE 28-11** ■ Mechanisms of disturbed liver function related to portal hypertension.

venous blood returning to the heart from the abdominal organs collects in the portal vein and travels through the liver before entering the vena cava. Portal hypertension can be caused by a variety of conditions that increase resistance to hepatic blood flow, including prehepatic, posthepatic, and intrahepatic obstructions (with *hepatic* referring to the liver lobules, rather than the entire liver).[6]

Prehepatic causes of portal hypertension include portal vein thrombosis and external compression caused by cancer or enlarged lymph nodes that produce obstruction of the portal vein before it enters the liver. *Posthepatic* obstruction refers to any obstruction to blood flow through the hepatic veins beyond the liver lobules, either within or distal to the liver. It is caused by conditions such as thrombosis of the hepatic veins, veno-occlusive disease, and severe right-sided heart failure that impede the outflow of venous blood from the liver. *Intrahepatic* causes of portal hypertension include conditions that cause obstruction of blood flow within the liver. In alcoholic cirrhosis, which is the major cause of portal hypertension, bands of fibrous tissue and fibrous nodules distort the architecture of the liver and increase the resistance to portal blood flow, which leads to portal hypertension.

Complications of portal hypertension arise from the increased pressure and dilatation of the venous channels behind the obstruction. In addition, collateral channels open that connect the portal circulation with the systemic circulation. The major complications of the increased portal vein pressure and the opening of collateral channels are ascites, splenomegaly,



■ **FIGURE 28-12** ■ Collateral abdominal veins on the anterior abdominal wall in a patient with alcoholic liver disease as recorded by black and white photography (**top**) and infrared photography (**bottom**). (Schiff L. [1982]. *Diseases of the liver.* Philadelphia: J.B. Lippincott)

KEY CONCEPTS

PORTAL HYPERTENSION

- Venous blood from the gastrointestinal tract empties into the portal vein and travels through the liver before moving into the general venous circulation.
- Obstruction of blood flow and development of portal hypertension produces an increase in the hydrostatic pressure within the peritoneal capillaries, contributing to the development of ascites, splenic engorgement with sequestration and destruction of blood cells and platelets, and shunting of blood to collateral venous channels causing varicosities of the hemorrhoidal and esophageal veins.

and the formation of portosystemic shunts with bleeding from esophageal varices (Fig. 28-11).

Ascites. Ascites occurs when the amount of fluid in the peritoneal cavity is increased and is a late-stage manifestation of cirrhosis and portal hypertension.[31] It is not uncommon for persons with advanced cirrhosis to present with an accumulation of 15 L or more of ascitic fluid. Those who gain this much fluid often experience abdominal discomfort, dyspnea, and insomnia.

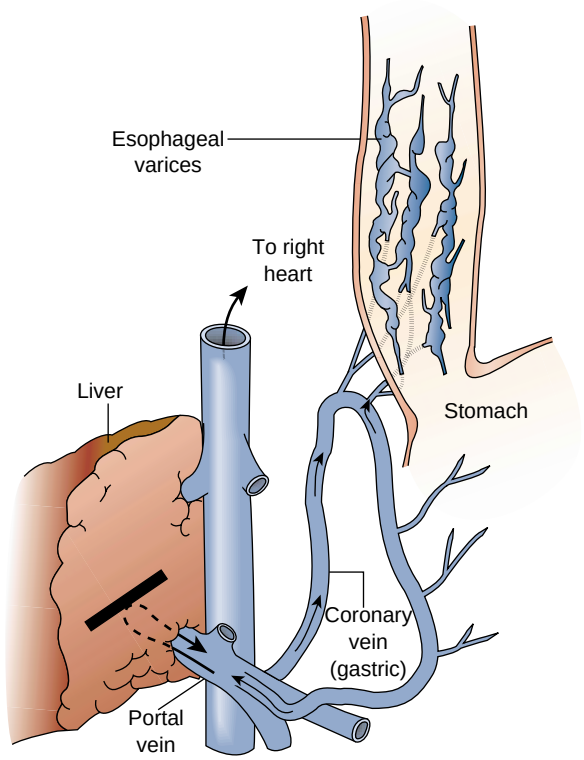
Although the mechanisms responsible for the development of ascites are not completely understood, several factors seem to contribute to fluid accumulation, including an increase in capillary pressure caused by portal hypertension and obstruction of venous flow through the liver, salt and water retention by the kidney, and decreased colloidal osmotic pressure caused by impaired synthesis of albumin by the liver (see Chapter 6).

Treatment of ascites usually focuses on dietary restriction of sodium and administration of diuretics. Water intake also may need to be restricted. Because of the many limitations in sodium restriction, the use of diuretics has become the mainstay of treatment for ascites. Oral potassium supplements often are given to prevent hypokalemia. The upright position is associated with the activation of the renin-angiotensin-aldosterone system; therefore, bed rest may be recommended for persons with a large amount of ascites.[32] Large-volume paracentesis (removal of 5 L or more of ascitic fluid) may be done in persons with massive ascites and pulmonary compromise.

Splenomegaly. The spleen enlarges progressively in portal hypertension because of shunting of blood into the splenic vein. The enlarged spleen often gives rise to sequestering of significant numbers of blood elements and development of a syndrome known as *hypersplenism*. Hypersplenism is characterized by a decrease in the life span and a subsequent decrease in all the formed elements of the blood, leading to anemia, thrombocytopenia, and leukopenia. The person with thrombocytopenia is subject to purpura, easy bruising, hematuria, and abnormal menstrual bleeding, and is vulnerable to bleeding from the esophagus and other segments of the gastrointestinal tract.

Portosystemic Shunts. With the gradual obstruction of venous blood flow in the liver, the pressure in the portal vein increases, and large collateral channels develop between the portal and systemic veins that supply the lower rectum and esophagus and the umbilical veins of the falciform ligament that attaches to the anterior wall of the abdomen. The collaterals between the inferior and internal iliac veins may give rise to hemorrhoids. In some persons, the fetal umbilical vein is not totally obliterated; it forms a channel on the anterior abdominal wall (Fig. 28-12). Dilated veins around the umbilicus are called *caput medusae*. Portopulmonary shunts also may develop and cause blood to bypass the pulmonary capillaries, interfering with blood oxygenation and producing cyanosis.

Clinically, the most important collateral channels are those connecting the portal and coronary veins that lead to reversal of flow and formation of thin-walled varicosities in the submucosa of the esophagus (Fig. 28-13). These thin-walled *esophageal varices* are subject to rupture, producing massive and sometimes fatal hemorrhage. Impaired hepatic synthesis of coagulation factors and decreased platelet levels (*i.e.*, thrombocytopenia) caused by splenomegaly may further complicate the control of esophageal bleeding. Esophageal varices develop in approximately 65% of persons with advanced cirrhosis and cause massive hemorrhage and death in approximately half of them.[5]



■ **FIGURE 28-13** ■ Obstruction of blood flow in the portal circulation, with portal hypertension and diversion of blood flow to other venous channels, including the gastric and esophageal veins.

Treatment of portal hypertension and esophageal varices is directed at prevention of initial hemorrhage, management of acute hemorrhage, and prevention of recurrent variceal hemorrhage. Mechanical compression of the bleeding vessel may be accomplished through the use of an esophageal balloon, designed to compress the bleeding vessel. Prevention of recurrent hemorrhage focuses on lowering portal venous pressure and diverting blood flow away from the easily ruptured collateral channels. Pharmacologic therapy is used to lower portal venous pressure and prevent initial hemorrhage. β-Adrenergic–blocking drugs (*e.g.*, propranolol) commonly are used for this purpose. Endoscopic sclerotherapy and band ligation is used to prevent rebleeding. Portosystemic shunt procedures involve the creation of an opening between the portal vein and a systemic vein as a means of bypassing the liver. The transjugular intrahepatic portosystemic shunt (TIPS) procedure involves the placement of an expandable metal stent between a branch of the hepatic and portal vein inserted via the internal jugular vein.

Liver Failure

The most severe clinical consequence of liver disease is hepatic failure. It may result from sudden and massive hepatic destruction, as in fulminant hepatitis, or it may be the result of

progressive damage to the liver, such as occurs in alcoholic cirrhosis. Whatever the cause, 80% to 90% of hepatic functional capacity must be lost before hepatic failure occurs.[5] In many cases, the progressive decompensating aspects of the disease are hastened by intercurrent conditions, such as gastrointestinal bleeding, systemic infection, electrolyte disturbances, or superimposed diseases such as heart failure.

The manifestations of liver failure reflect the various synthesis, storage, metabolic, and excretory functions of the liver, (Fig. 28-14). *Fetor hepaticus* refers to a characteristic musty, sweetish odor of the breath in the patient with advanced liver failure, resulting from the metabolic by-products of the intestinal bacteria.

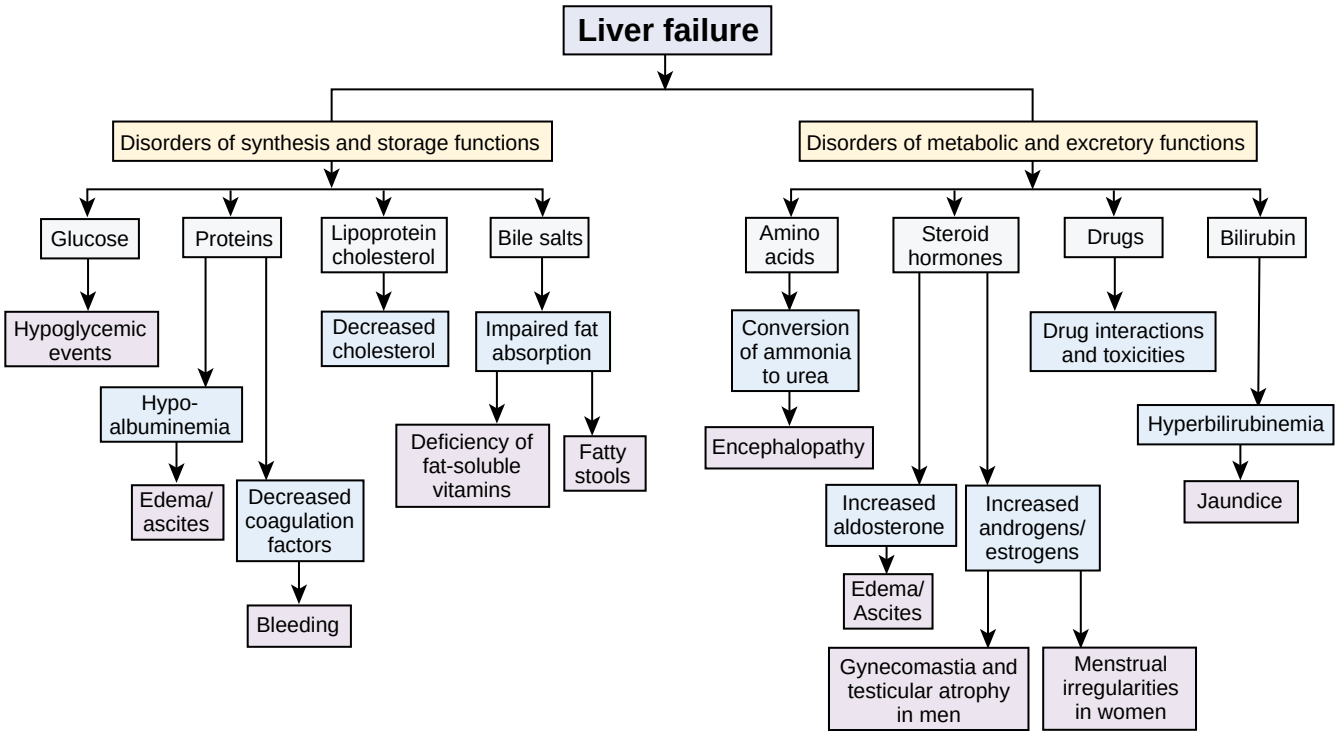
Hematologic Disorders. Liver failure can cause anemia, thrombocytopenia, coagulation defects, and leukopenia. Anemia may be caused by blood loss, excessive red blood cell destruction, and impaired formation of red blood cells. A folic acid deficiency may lead to severe megaloblastic anemia. Changes in the lipid composition of the red cell membrane increase hemolysis. Because factors V, VII, IX, and X, prothrombin, and fibrinogen are synthesized by the liver, their decline in liver disease contributes to bleeding disorders. Malabsorption of the fat-soluble vitamin K contributes further to the impaired synthesis of these clotting factors.

Endocrine Disorders. The liver metabolizes the steroid hormones. Endocrine disorders, particularly disturbances in gonadal function, are common accompaniments of cirrhosis and liver failure. Women may have menstrual irregularities (usually amenorrhea), loss of libido, and sterility. In men, testosterone levels usually fall, the testes atrophy, and loss of libido, impotence, and gynecomastia occur. A decrease in aldosterone metabolism may contribute to salt and water retention by the kidney, along with a lowering of serum potassium resulting from increased elimination of potassium.

Skin Disorders. Liver failure brings on numerous skin disorders. These lesions, called variously *vascular spiders, telangiectases, spider angiomas,* and *spider nevi*, are seen most often in the upper half of the body. They consist of a central pulsating arteriole from which smaller vessels radiate. Palmar erythema is redness of the palms, probably caused by increased blood flow from higher cardiac output. Clubbing of the fingers may be seen in persons with cirrhosis. Jaundice usually is a late manifestation of liver failure.

Hepatorenal Syndrome. The hepatorenal syndrome refers to a functional state of renal failure sometimes seen during the terminal stages of liver failure with ascites. It is characterized by progressive azotemia, increased serum creatinine levels, and oliguria. Although the basic cause is unknown, a decrease in renal blood flow is believed to play a part. Ultimately, when renal failure is superimposed on liver failure, azotemia and elevated levels of blood ammonia occur; this condition is thought to contribute to hepatic encephalopathy and coma.

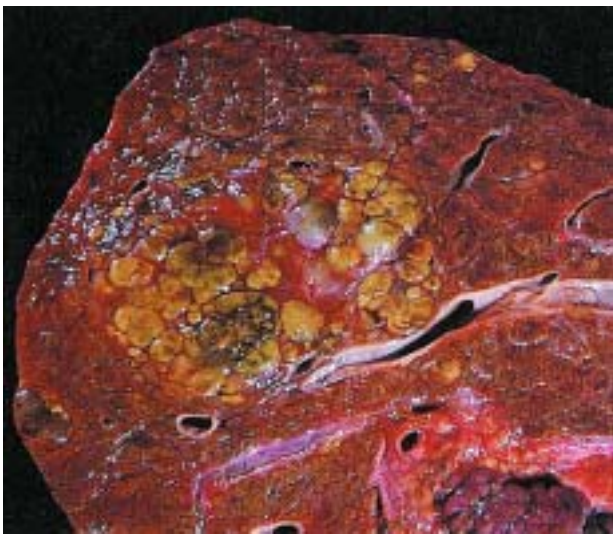
Hepatic Encephalopathy. Hepatic encephalopathy refers to the totality of central nervous system manifestations of liver failure. It is characterized by neural disturbances ranging from a lack of mental alertness to confusion, coma, and convulsions. A very early sign of hepatic encephalopathy is a flapping tremor



■ **FIGURE 28-14** ■ Alterations in liver function and manifestations of liver failure.

called *asterixis*. Various degrees of memory loss may occur, coupled with personality changes such as euphoria, irritability, anxiety, and lack of concern about personal appearance and self. Speech may be impaired, and the patient may be unable to perform certain purposeful movements. The encephalopathy may progress to decerebrate rigidity and then to a terminal deep coma.

Although the cause of hepatic encephalopathy is unknown, the accumulation of neurotoxins, which appear in the blood because the liver has lost its detoxifying capacity, is believed to be a factor. Hepatic encephalopathy develops in approximately 10% of persons with portosystemic shunts. One of the suspected neurotoxins is ammonia. A particularly important function of the liver is the conversion of ammonia, a by-product of protein and amino acid metabolism, to urea. The ammonium ion is produced in abundance in the intestinal tract, particularly in the colon, by the bacterial degradation of luminal proteins and amino acids. Normally, these ammonium ions diffuse into the portal blood and are transported to the liver, where they are converted to urea before entering the general circulation. When the blood from the intestine bypasses the liver or the liver is unable to convert ammonia to urea, ammonia moves directly into the general circulation and then into the cerebral circulation. Hepatic encephalopathy may become worse after a large protein meal or gastrointestinal tract bleeding.



■ **FIGURE 28-15** ■ Hepatocellular carcinoma. Cross-section of a cirrhotic liver showing a poorly circumscribed, nodular area of yellow, partially hemorrhagic carcinoma. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 826]. Philadelphia: Lippincott Williams & Wilkins)

Treatment. The treatment of liver failure is directed toward eliminating alcohol intake when the condition is caused by alcoholic cirrhosis; preventing infections; providing sufficient carbohydrates and calories to prevent protein breakdown; correcting fluid and electrolyte imbalances, particularly hypokalemia; and decreasing ammonia production in the gastrointestinal tract by controlling protein intake. In many cases, liver transplantation remains the only effective treatment.

Cancer of the Liver

Primary liver tumors are relatively rare in the United States, accounting for approximately 0.5% to 2% of all cancers.[3] The American Cancer Society estimates that more than 17,300 new cases of primary liver and intrahepatic cancer will be diagnosed during 2003, and more than 14,400 people will die of the disease during the same period.[33] In contrast to many other cancers, the number of people who have liver cancer and die of it is increasing. Liver cancer is approximately 10 times more common in developing countries in Southeast Asia and Africa. In many of these countries, it is the most common type of cancer.

There are two major types of primary liver cancer: hepatocellular carcinoma, which arises from the liver cells (Fig. 28-15), and cholangiocarcinoma, which is a primary cancer of bile duct cells.[5] Hepatocellular cancer is one of the few cancers for which an underlying etiology can be identified in most cases and is unique because it usually occurs in a background of chronic liver disease.[34] Among the factors identified as etiologic agents in hepatocellular cancer are chronic viral hepatitis (HBV, HCV, HDV), cirrhosis, long-term exposure to aflatoxin, and drinking water contaminated with arsenic. With HBV and HCV, both of which become integrated into the host DNA, repeated cycles of cell death and regeneration afford the potential for development of cancer-producing mutations. Aflatoxins, produced by food spoilage molds in certain areas endemic for hepatocellular carcinoma, are particularly potent carcinogenic agents.[5] These carcinogenic agents are activated by hepatocytes and their products incorporated into the host DNA with the potential for producing cancer-producing mutations.

The manifestations of hepatocellular cancer often are insidious in onset and masked by those related to cirrhosis or chronic hepatitis. The initial symptoms include weakness, anorexia, weight loss, fatigue, bloating, a sensation of abdominal fullness, and a dull, aching abdominal pain. Ascites, which often obscures weight loss, is common. Jaundice, if present, usually is mild. There may be a rapid increase in liver size and worsening of ascites in persons with pre-existing cirrhosis. Usually, the liver is enlarged when these symptoms appear, and there is a low fever without apparent cause. Serum α-fetoprotein, a serum protein present during fetal life, normally is barely detectable in the serum after the age of 2 years, but it is present in 60% to 75% of cases of hepatocellular carcinoma.[5]

Cholangiocarcinoma occurs much less frequently than hepatocellular carcinoma. The etiology, clinical features, and prognosis vary considerably with the part of the biliary tree that is the site of origin. Cholangiocarcinoma is not associated with the same risk factors as hepatocellular carcinoma. Instead, most of the risk factors revolve around longstanding inflammation and injury of the bile duct epithelium. Cholangiocarcinoma often presents with pain, weight loss, anorexia, and abdominal swelling or awareness of a mass in the right hypochondrium. Tumors affecting the central or distal bile ducts may present with jaundice.

Primary cancers of the liver usually are far advanced at the time of diagnosis; the 5-year survival rate is approximately 1%, and most patients die within 6 months. The treatment of choice is subtotal hepatectomy, if conditions permit. Chemotherapy and radiation therapy are largely palliative. Although

liver transplantation may be an option for people with well-compensated cirrhosis and small tumors, it often is impractical because of the shortage of donor organs.

Metastatic tumors of the liver are much more common than primary tumors. Common sources include colorectal cancer and spread from the breast, lung, or urogenital cancers. In addition, tumors of neuroendocrine origin spread to the liver. It often is difficult to distinguish primary from metastatic tumors with the use of CT scans, MRI, or ultrasonography. Usually the diagnosis is confirmed by biopsy.

In summary, the liver is subject to most of the disease processes that affect other body structures, such as vascular disorders, inflammation, metabolic diseases, toxic injury, and neoplasms.

Hepatitis is characterized by inflammation of the liver. Acute viral hepatitis is caused by hepatitis viruses A, B, C, D, and E. Although all these viruses cause acute hepatitis, they differ in terms of mode of transmission, incubation period, mechanism, degree and chronicity of liver damage, and the ability to evolve to a carrier state. HBV, HCV, and HDV have the potential for progression to the carrier state, chronic hepatitis, and hepatocellular carcinoma.

Intrahepatic biliary diseases disrupt the flow of bile through the liver, causing cholestasis and biliary cirrhosis. Among the causes of intrahepatic biliary diseases are primary biliary cirrhosis, primary sclerosing cholangitis, and secondary biliary cirrhosis.

Because alcohol competes for use of intracellular cofactors normally needed by the liver for other metabolic processes, it tends to disrupt the metabolic functions of the liver. The spectrum of alcoholic liver disease includes fatty liver disease, alcoholic hepatitis, and cirrhosis.

Cirrhosis represents the end stage of chronic liver disease in which much of the functional liver tissue has been replaced by fibrous tissue. The fibrous tissue replaces normally functioning liver tissue and forms constrictive bands that disrupt flow in the vascular channels and biliary duct systems of the liver. The disruption of vascular channels predisposes to portal hypertension and its complications, loss of liver cells, and eventual liver failure. Portal hypertension is characterized by increased resistance to flow and increased pressure in the portal venous system; the pathologic consequences of the disorder include ascites, the formation of collateral bypass channels (*e.g.*, esophageal varices) from the portosystemic circulation, and splenomegaly. Liver failure represents the end stage of a number of liver diseases and occurs when less than 10% of liver tissue is functional. The manifestations of liver failure reflect the various functions of the liver, including hematologic disorders, disruption of endocrine function, skin disorders, hepatorenal syndrome, and hepatic encephalopathy.

Cancers of the liver include metastatic and primary neoplasms. Primary hepatic neoplasms are rare, accounting for less than 2% of cancers, and those involving the hepatocytes or liver cells are commonly associated with underlying diseases of the liver such as cirrhosis and chronic hepatitis. Liver cancer usually is far advanced at the time of diagnosis; the 5-year survival rate is approximately 1%.

DISORDERS OF THE GALLBLADDER AND EXTRAHEPATIC BILE DUCTS

The so-called hepatobiliary system consists of the gallbladder, the left and right hepatic ducts, which come together to form the common hepatic duct, the cystic duct, which extends to the gallbladder, and the common bile duct, which is formed by the union of the common hepatic duct and the cystic duct (see Fig. 28-16). The common bile duct descends posterior to the first part of the duodenum, where it comes in contact with the main pancreatic duct. These ducts unite to form the hepatopancreatic ampulla (ampulla of Vater). The circular muscle around the distal end of the bile duct is thickened to form the sphincter of the bile duct (Fig. 28-16).

The gallbladder is a distensible, pear-shaped, muscular sac located on the ventral surface of the liver. It has a outer serous peritoneal layer, a middle smooth muscle layer, and an inner mucosal layer that is continuous with the linings of the bile duct. The function of the gallbladder is to store and concentrate bile. Bile contains bile salts, cholesterol, bilirubin, lecithin, fatty acids, water, and the electrolytes normally found in the plasma. The cholesterol found in bile has no known function; it is assumed to be a by-product of bile salt formation, and its presence is linked to the excretory function of bile. Normally insoluble in water, cholesterol is rendered soluble by the action of bile salts and lecithin, which combine with it to form micelles. In the gallbladder, water and electrolytes are absorbed from the liver bile, causing the bile to become more concentrated. Because neither lecithin nor bile salts are absorbed in the gallbladder, their concentration increases along with that of cholesterol; in this way, the solubility of cholesterol is maintained.

Entrance of food into the intestine causes the gallbladder to contract and the sphincter of the bile duct to relax, such that bile stored in the gallbladder moves into the duodenum. The stimulus for gallbladder contraction is primarily hormonal. Products of food digestion, particularly lipids, stimulate the release of a gastrointestinal hormone called cholecystokinin from the mucosa of the duodenum. Cholecystokinin provides a strong stimulus for gallbladder contraction. The role of other gastrointestinal hormones in bile release is less clearly understood.

Cholelithiasis and Cholecystitis

Two common disorders of the gallbladder system are cholelithiasis (*i.e.*, gallstones) and inflammation of the gallbladder (cholecystitis) or common bile duct (cholangitis). At least 10% of adults have gallstones. Approximately twice as many women as men have gallstones, and there is an increased prevalence with age—after 60 years of age, 10% to 15% among men and 20% to 40% among women.[35]

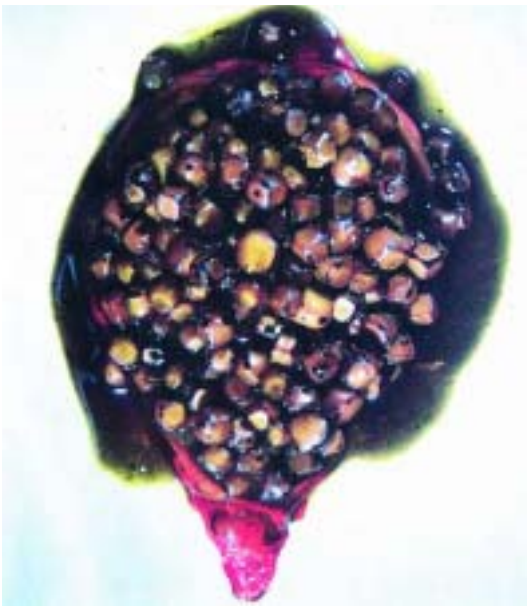
Cholelithiasis

Gallstones are caused by precipitation of substances contained in bile, mainly cholesterol and bilirubin. The bile of which gallstones are formed usually is supersaturated with cholesterol or bilirubin. Approximately 75% of gallstones are composed primarily of cholesterol; the other 25% are black or brown pigment stones consisting of calcium salts with bilirubin.[35] Many

■ **FIGURE 28-16** ■ (**A**) Extrahepatic bile passages, gallbladder, and pancreatic ducts. (**B**) Entry of bile duct and pancreatic duct into the hepatopancreatic ampulla, which opens into the duodenum.

stones have a mixed composition. Figure 28-17 shows a gallbladder with numerous cholesterol gallstones.

Three factors contribute to the formation of gallstones: (1) abnormalities in the composition of bile, (2) stasis of bile, and (3) inflammation of the gallbladder. The formation of cholesterol stones is associated with obesity and occurs more frequently in women, especially women who have had multiple pregnancies or who are taking oral contraceptives. All of these factors cause the liver to excrete more cholesterol into the bile. Estrogen reduces the synthesis of bile acid in women. Drugs that lower serum cholesterol levels, such as clofibrate, also cause increased cholesterol excretion into the bile. Malabsorption disorders stemming from ileal disease or intestinal bypass surgery interfere with intestinal reabsorption of bile salts, which are needed to maintain cholesterol solubility. Gallbladder sludge (thickened gallbladder mucoprotein with tiny trapped cholesterol crystals) causes stasis of bile flow and is thought to be a precursor of gallstones. Sludge frequently occurs with pregnancy, starvation, and rapid weight loss.[35] Inflammation of the gallbladder alters the absorptive characteristics of the mucosal layer, allowing excessive absorption of water and bile salts. Cholesterol gallstones are extremely common among Native Americans, which suggests that a genetic component may have a role in gallstone formation. Pigment



■ **FIGURE 28-17** ■ Cholesterol gallstones. The gallbladder has been opened to reveal numerous yellow cholesterol gallstones (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 791]. Philadelphia: Lippincott Williams & Wilkins)

stones containing bilirubin are seen in persons with hemolytic disease (*e.g.*, sickle cell disease) and hepatic cirrhosis.

Many persons with gallstones have no symptoms. Gallstones cause symptoms when they obstruct bile flow. Small stones (*e.g.*, <8 mm in diameter) pass into the common duct, producing symptoms of indigestion and biliary colic. Larger stones are more likely to obstruct flow and cause jaundice. The pain of biliary colic usually is abrupt in onset and increases steadily in intensity until it reaches a climax in 30 to 60 minutes. It is usually located in the upper right quadrant or epigastric area and is often referred to the back, above the waist or to the right shoulder and scapula region. The pain usually persists for 2 to 8 hours and is followed by soreness in the upper right quadrant.

Acute and Chronic Cholecystitis

The term *cholecystitis* refers to inflammation of the gallbladder. Both acute and chronic cholecystitis are associated with cholelithiasis. Acute cholecystitis may be superimposed on chronic cholecystitis.

Acute cholecystitis almost always is associated with complete or partial obstruction. It is believed that the inflammation is caused by chemical irritation from the concentrated bile, along with mucosal swelling and ischemia resulting from venous congestion and lymphatic stasis. The gallbladder usually is markedly distended. Bacterial infections may arise secondary to the ischemia and chemical irritation. The bacteria reach the injured gallbladder through the blood, lymphatics, or bile ducts or from adjacent organs. Among the common pathogens are staphylococci and enterococci. The wall of the gallbladder is most vulnerable to the effects of ischemia, as a result of which mucosal necrosis and sloughing occur. The process may lead to gangrenous changes and perforation of the gallbladder.

The signs and symptoms of acute cholecystitis vary with the severity of obstruction and inflammation. Pain, initially similar to that of biliary colic, is characteristic of acute cholecystitis. It often is precipitated by a fatty meal and may initiate with complaints of indigestion. However, it does not subside spontaneously and responds poorly or only temporarily to potent analgesics. When the inflammation progresses to involve the peritoneum, the pain becomes more pronounced in the right upper quadrant. The right subcostal region is tender, and the muscles that surround the area spasm. Approximately 75% of patients have vomiting, and approximately 25% have jaundice.[22] Fever and an abnormally high white blood cell count attest to inflammation. Total serum bilirubin, aminotransferase, and alkaline phosphatase levels usually are elevated.

Chronic cholecystitis results from repeated episodes of acute cholecystitis or chronic irritation of the gallbladder by stones. It is characterized by varying degrees of chronic inflammation. Gallstones almost always are present. Cholelithiasis with chronic cholecystitis may be associated with acute exacerbations of gallbladder inflammation, common duct stones, pancreatitis, and rarely, carcinoma of the gallbladder.

The manifestations of chronic cholecystitis are more vague than those of acute cholecystitis. There may be intolerance to fatty foods, belching, and other indications of discomfort. Often, there are episodes of colicky pain with obstruction of biliary flow caused by gallstones. The gallbladder, which in chronic cholecystitis usually contains stones, may be enlarged, shrunken, or of normal size.

Diagnosis and Treatment. The most commonly used methods for diagnosis of gallbladder disease include ultrasonography and nuclear scanning (cholescintigraphy).[35] Ultrasonography is widely used in diagnosing gallbladder disease. It can detect stones as small as 1 to 2 cm, and its overall accuracy in detecting gallbladder disease is high. In addition to stones, ultrasonography can detect wall thickening, which indicates inflammation. Cholescintigraphy, also called a *gallbladder scan*, relies on the ability of the liver to extract a rapidly injected radionuclide, technetium-99m, bound to one of several iminodiacetic acids, that is excreted into the bile ducts. The gallbladder scan is highly accurate in detecting acute cholecystitis.

Gallbladder disease usually is treated by removing the gallbladder or by dissolving the stones or fragmenting them. Laparoscopic cholecystectomy has largely become the treatment of choice for symptomatic gallbladder disease.

Choledocholithiasis and Cholangitis

Choledocholithiasis refers to stones in the common duct and cholangitis to inflammation of the common duct. Common duct stones usually originate in the gallbladder but can form spontaneously in the common duct. The stones frequently are clinically silent unless there is obstruction.

The manifestations of choledocholithiasis are similar to those of gallstones and acute cholecystitis. There is a history of acute biliary colic and right upper abdominal pain, with chills, fever, and jaundice associated with episodes of abdominal pain. Bilirubinuria and an elevated serum bilirubin are present if the common duct is obstructed.

Complications include acute suppurative cholangitis accompanied by pus in the common duct. It is characterized by the presence of an altered sensorium, lethargy, and septic shock.[22] Acute suppurative cholangitis represents an endoscopic or surgical emergency. Common duct stones also can obstruct the outflow of the pancreatic duct, causing a secondary pancreatitis.

Diagnostic measures include the use of ultrasonography, CT scans, and radionuclide to detect dilatation of the bile ducts and impaired blood flow. Endoscopic ultrasonography and magnetic resonance cholangiography may be used for detecting common duct stones. Both percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) provide a direct means for determining the cause, location, and extent of obstruction. PTC involves the injection of dye directly into the biliary tree. It requires the insertion of a thin, flexible needle through a small incision in the skin with advancement into the biliary tree. ERCP involves the passage of an endoscope into the duodenum and the passage of a catheter into the hepatopancreatic ampulla. ERCP can be used to enlarge the opening of the bile duct sphincter so that a lodged stone can pass into the intestine or an instrument may be inserted into the common duct to remove the stone.

Common duct stones in persons with cholelithiasis usually are treated by stone extraction followed by laparoscopic cholecystectomy. Antibiotic therapy, with an agent that penetrates the bile, is used to treat the infection. Emergency decompression of the common duct, usually by ERCP, may be necessary for persons who are septic or fail to experience improvement with antibiotic treatment.

Cancer of the Gallbladder

Cancer of the gallbladder is found in approximately 2% of persons operated on for biliary tract disease. The onset of symptoms usually is insidious, and they resemble those of cholecystitis; the diagnosis often is made unexpectedly at the time of gallbladder surgery. Because of their ability to produce chronic irritation of the gallbladder mucosa, it is believed that gallstones play a role in the development of gallbladder cancer. The 5-year survival rate is only approximately 3%.[5]

In summary, the biliary tract serves as a passageway for the delivery of bile from the liver to the intestine. This tract consists of the bile ducts and gallbladder. The most common causes of biliary tract disease are cholelithiasis and cholecystitis. Three factors contribute to the development of cholelithiasis: abnormalities in the composition of bile, stasis of bile, and inflammation of the gallbladder. Cholelithiasis predisposes to obstruction of bile flow, causing biliary colic and acute or chronic cholecystitis. Cancer of the gallbladder, which has a poor 5-year survival rate, occurs in 2% of persons with biliary tract disease.

DISORDERS OF THE EXOCRINE PANCREAS

The pancreas lies transversely in the posterior part of the upper abdomen. The head of the pancreas is at the right of the abdomen; it rests against the curve of the duodenum in the area of the hepatopancreatic ampulla and its entrance into the duodenum (Fig. 28-1). The body of the pancreas lies beneath the stomach. The tail touches the spleen. The pancreas is virtually hidden because of its posterior position; unlike many other organs, it cannot be palpated. Because of the position of the pancreas and its large functional reserve, symptoms from conditions such as cancer of the pancreas do not usually appear until the disorder is far advanced.

The pancreas is both an endocrine and exocrine organ. Its function as an endocrine organ is discussed in Chapter 31. The exocrine pancreas is made up of lobules that consist of acinar cells, which secrete digestive enzymes into a system of microscopic ducts. These ducts empty into the main pancreatic duct, which extends from left to right through the substance of the pancreas. The main pancreatic duct and the bile duct unite to form the hepatopancreatic ampulla, which empties into the duodenum. The sphincter of the pancreatic duct controls the flow of pancreatic secretion into duodenum (Fig. 28-16).

The pancreatic secretions contain proteolytic enzymes that break down dietary proteins, including trypsin, chymotrypsin, carboxypolypeptidase, ribonuclease, and deoxyribonuclease. The pancreas also secretes pancreatic amylase, which breaks down starch, and lipases, which hydrolyze neutral fats into glycerol and fatty acids. The pancreatic enzymes are secreted in the inactive form and become activated in the intestine. This is important because the enzymes would digest the tissue of the pancreas itself if they were secreted in the active form. The acinar cells secrete a trypsin inhibitor, which prevents trypsin activation. Because trypsin activates other proteolytic enzymes, the trypsin inhibitor prevents subsequent activation of those other enzymes. The smaller pancreatic ducts are lined with epithelial cells that secrete water and bicarbonate and thereby modify the fluid and electrolyte composition of the pancreatic secretions. Two types of pancreatic disease are discussed in this chapter: acute and chronic pancreatitis and cancer of the pancreas.

Acute Pancreatitis

Acute pancreatitis represents an inflammation of the pancreas that ranges from a mild self-limited disease, consisting of inflammation and interstitial edema, to an acute hemorrhagic pancreatitis that is associated with massive necrosis of tissue.[36] Acute hemorrhagic pancreatitis is a severe, life-threatening disorder associated with the escape of activated pancreatic enzymes into the pancreas and surrounding tissues. These enzymes cause fat necrosis, or autodigestion, of the pancreas and produce fatty deposits in the abdominal cavity with hemorrhage from the necrotic vessels.

Although a number of factors are associated with the development of acute pancreatitis, most cases result from gallstones (stones in the common duct) or alcohol abuse.[37,38] In the case of biliary tract obstruction caused by gallstones, pancreatic duct obstruction or biliary reflux is believed to activate the enzymes in the pancreatic duct system. The precise mechanisms whereby alcohol exerts its action are largely unknown. Alcohol is known to be a potent stimulator of pancreatic secretions, and it also is known to cause constriction of the sphincter of the pancreatic duct. Acute pancreatitis also is associated with hyperlipidemia, hyperparathyroidism, infections (particularly viral), abdominal and surgical trauma, and drugs such as steroids and thiazide diuretics.

The onset of acute pancreatitis usually is abrupt and dramatic, and it may follow a heavy meal or an alcoholic binge. The most common initial symptom is severe epigastric and abdominal pain that radiates to the back. The pain is aggravated when the person is lying supine; it is less severe when the person is sitting and leaning forward. Abdominal distention accompanied by hypoactive bowel sounds is common. An important disturbance related to acute necrotizing pancreatitis is the loss of a large volume of fluid into the retroperitoneal and peripancreatic spaces and the abdominal cavity. Tachycardia, hypotension, cool and clammy skin, and fever often are evident. Signs of hypocalcemia may develop, probably as a result of the precipitation of serum calcium in the areas of fat necrosis. Mild jaundice may appear after the first 24 hours because of biliary obstruction. Complications include acute respiratory distress syndrome and acute tubular necrosis. Hypocalcemia occurs in approximately 25% of patients.

Total serum amylase is the test used most frequently in the diagnosis of acute pancreatitis. Serum amylase levels increase within the first 24 hours after onset of symptoms and remain elevated for 48 to 72 hours. The serum lipase level also increases during the first 24 to 48 hours and remains elevated for 5 to 14 days. Urinary clearance of amylase is increased. Because the serum amylase level may be increased as a result of other serious illnesses, the urinary level of amylase is often measured. The white blood cell count may be increased, and blood glucose and serum bilirubin levels may be elevated. Plain radiographs of the abdomen may be used for detecting gallstones

or abdominal complications. CT scans and dynamic contrast-enhanced CT of the pancreas are used to detect necrosis and fluid accumulation.

The treatment consists of measures directed at pain relief, "putting the pancreas to rest," and restoration of lost plasma volume. Antibiotic prophylaxis is used to prevent infection of necrotic pancreatic tissue. Oral foods and fluids are withheld, and gastric suction is instituted to treat distention of the bowel and prevent further stimulation of the secretion of pancreatic enzymes. Intravenous fluids and electrolytes are administered to replace those lost from the circulation and to combat hypotension and shock. Intravenous colloid solutions are given to replace the fluid that has become sequestered in the abdomen and retroperitoneal space.

Persons who survive acute necrotizing pancreatitis are at risk for development of pancreatic abscesses and pseudocysts. A pseudocyst is a collection of degraded blood, debris, and necrotic pancreatic tissue enclosed in a layer of connective tissue (Fig. 28-18). The pseudocyst most often is connected to a pancreatic duct, so that it continues to increase in mass. The symptoms depend on its location; for example, jaundice may occur when a cyst develops near the head of the pancreas, close to the common duct. Pseudocysts may become secondarily infected and form an abscess. Pseudocysts may resolve or, if they persist, may require surgical intervention.

Chronic Pancreatitis

Chronic pancreatitis is characterized by progressive destruction of the pancreas. It can be divided into two types: chronic calcifying pancreatitis and chronic obstructive pancreatitis.[38] In chronic calcifying pancreatitis, calcified protein plugs (*i.e.*, calculi) form in the pancreatic ducts. This form is seen most often in alcoholics. Alcohol damages pancreatic cells directly and also increases the concentration of proteins in the pancreatic secretions, which eventually leads to formation of protein plugs.[39] Other causes of chronic pancreatitis are cystic fibrosis and chronic obstructive pancreatitis caused by stenosis of the sphincter of the pancreatic duct. In obstructive pancreatitis, lesions are more prominent in the head of the pancreas. The disease usually is caused by cholelithiasis and sometimes is relieved by removal of the stones.

Chronic pancreatitis is manifested in episodes that are similar, albeit of lesser severity, to those of acute pancreatitis. Patients have persistent, recurring episodes of epigastric and upper left quadrant pain; the attacks often are precipitated by alcohol abuse or overeating. Anorexia, nausea, vomiting, constipation, and flatulence are common. Eventually the disease progresses to the extent that endocrine and exocrine pancreatic functions become deficient. At this point, signs of diabetes mellitus and the malabsorption syndrome (*e.g.*, weight loss, fatty stools [steatorrhea]) become apparent.[38]

Treatment consists of measures to treat coexisting biliary tract disease. A low-fat diet usually is prescribed. The signs of malabsorption may be treated with pancreatic enzymes. When diabetes is present, it is treated with insulin. Alcohol is forbidden because it frequently precipitates attacks. Because of the frequent episodes of pain, narcotic addiction is a potential problem in persons with chronic pancreatitis. Surgical intervention sometimes is needed to relieve the pain and usually focuses on relieving any obstruction that may be present. In advanced cases, a subtotal or total pancreatectomy may be necessary.[22]

■ **FIGURE 28-18** ■ Pancreatic pseudocyst. A cystic cavity arises from the head of the pancreas. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 847]. Philadelphia: Lippincott Williams & Wilkins)

Cancer of the Pancreas

Pancreatic cancer is now the fourth leading cause of cancer death in the United States, with more than 28,000 deaths attributed to the neoplasm each year.[40] Considered to be one of the most deadly malignancies, pancreatic cancer is associated with a mortality:incidence ratio of approximately 0.99. The risk of pancreatic cancer increases after the age of 50 years, with most cases occurring between the ages of 60 and 80 years. The incidence and mortality rates for both male and female African Americans are higher than those for whites.

The cause of pancreatic cancer is unknown. Smoking appears to be a major risk factor.[41,42] The incidence of pancreatic cancer is twice as high among smokers than nonsmokers. The second most important factor appears to be diet. There appears to be an association of pancreatic cancer with an increasing total calorie intake and a high intake of fat, meat, salt, dehydrated foods, fried foods, refined sugars, soy beans, and nitrosamines. Data from animal studies indicate that nitrosamines and tobacco smoke are carcinogenic in the pancreas. A protective effect has been ascribed to a diet containing dietary fiber, vitamin C, fresh fruits and vegetables, and no preservatives. Diabetes and chronic pancreatitis also are associated with pancreatic cancer, although neither the nature nor the sequence of the possible cause-and-effect relation has been established.[41,42] Genetic alterations appear to play a role. There appears to be an association between pancreatic cancer and certain genetic disorders, including nonpolyposis colon cancer, familial breast cancer with the BRCA2 gene mutation (see Chapter 5), ataxia-telangiectasia syndrome, familial atypical multiple mole-melanoma syndrome, and hereditary pancreatitis.[41]

Cancer of the pancreas usually has an insidious onset. Pain, jaundice, and weight loss constitute the classic presentation of the disease. The most common pain is a dull epigastric pain often accompanied by back pain, often worse in the supine position, and relieved by sitting forward. Duodenal obstruction with nausea and vomiting is a late sign.

Because of the proximity of the pancreas to the common duct and the hepatopancreatic ampulla, cancer of the head of the pancreas tends to obstruct bile flow; this causes distention of the gallbladder and jaundice. Jaundice frequently is the presenting symptom of a person with cancer of the head of the

pancreas, and it usually is accompanied by complaints of pain and pruritus. Cancer of the body of the pancreas usually impinges on the celiac ganglion, causing pain. The pain usually worsens with ingestion of food or with assumption of the supine position. Cancer of the tail of the pancreas usually has metastasized before symptoms appear.

Ultrasonography and CT scanning are the most frequently used diagnostic methods to confirm the disease. Percutaneous fine-needle aspiration cytology of the pancreas has been one of the major advances in the diagnosis of pancreatic cancer. Endoscopic retrograde cholangiopancreatography may be used for evaluation of persons with suspected pancreatic cancer and obstructive jaundice.

Most cancers of the pancreas have metastasized by the time of diagnosis. Surgical resection of the tumor is done when the tumor is localized or as a palliative measure. Radiation therapy may be useful when the disease is not resectable but appears to be localized. The use of irradiation and chemotherapy for pancreatic cancer continues to be investigated. Pain control is one of the most important aspects in the management of persons with end-stage pancreatic cancer.

In summary, the pancreas is an endocrine and exocrine organ. The exocrine pancreas produces digestive enzymes that are secreted in an inactive form and transported to the small intestine through the main pancreatic duct, which usually empties into the ampulla of Vater and then into the duodenum through the sphincter of Oddi. Acute and chronic types of pancreatitis are associated with biliary reflux and chronic alcoholism. Acute pancreatitis is a dramatic and life-threatening disorder in which there is autodigestion of pancreatic tissue. Chronic pancreatitis causes progressive destruction of the endocrine and exocrine pancreas. It is characterized by episodes of pain and epigastric distress that are similar to but less severe than those that occur with acute pancreatitis. Cancer of the pancreas is the fourth leading cause of death in the United States. It usually is far advanced at the time of diagnosis, and the 5-year survival rate is less than 3%.

REVIEW QUESTIONS

- Characterize the function of the liver in terms of bilirubin elimination and describe the pathogenesis of unconjugated and conjugated hyperbilirubinemia.
- Relate the mechanism of bile formation and elimination to the development of cholestasis.
- Compare hepatitis A, B, C, D, and E in terms of source of infection, incubation period, acute disease manifestations, development of chronic disease, and the carrier state.
- Define the term *chronic hepatitis* and compare the pathogenesis of chronic autoimmune and chronic viral hepatitis.
- Explain the metabolism of alcohol by the liver and state the metabolic mechanisms that can be used to explain liver injury.
- Describe the pathogenesis of intrahepatic biliary tract disease.
- Characterize the liver changes that occur with cirrhosis.
- Describe the physiologic basis for portal hypertension and relate it to the development of ascites, esophageal varices, and splenomegaly.
- Relate the functions of the liver to the manifestations of liver failure.
- Relate the function of the gallbladder to the development of gallstones.
- Describe the clinical manifestations of acute and chronic cholecystitis.
- Characterize the effects of choledocholithiasis and cholangitis on bile flow and the potential for hepatic and pancreatic complications.
- Compare the causes and manifestations of acute and chronic pancreatitis.
- State the reason for the poor prognosis in pancreatic cancer.

connection

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