Alcohol Metabolism

Alcohol is readily absorbed from the stomach and intestine. It is then distributed to all of the tissues and fluids in the body in direct proportion to the blood level. Most of the alcohol that a person drinks (80% and 90%) is metabolized by the liver. In the liver, alcohol metabolism proceeds simultaneously by two major pathways: the alcohol dehydrogenase (ADH) system and the microsomal ethanol-oxidizing system (MEOS).27–29

The main enzyme system involved in alcohol metabolism is ADH, an enzyme located in the cytosol of hepatocytes. In the ADH-mediated oxidation of alcohol, both acetaldehyde and hydrogen (H+) are produced. The reaction involves a reduction in the adenine dinucleotide (NAD–to–nicotinamide adenine dinucleotide (NADH) ratio (see Chapter 1, Understanding Cell Metabolism), with a consequent decrease in NAD and increase in NADH. Since NAD is required for fatty acid oxidation, its deficiency is a main cause of the accumulation of fat in the liver of alcoholics. It also causes lactic acidosis in alcoholics.
Metabolism of alcohol by the MEOS system involves the CYP drug-metabolizing enzymes, located in the smooth endoplasmic reticulum. One of these metabolizing enzymes also oxidizes a number of other compounds, including various drugs (e.g., acetaminophen, isoniazid), toxins (e.g., carbon tetrachloride, halothane), industrial solvents, and carcinogenic agents (e.g., aflatoxin, nitrosamines). Induction of this system by alcohol enhances the susceptibility of alcoholics to the hepatotoxic effects of these and other compounds metabolized by the same system.29

The metabolic end products of alcohol metabolism (e.g., acetaldehyde, free radicals) are responsible for a variety of metabolic alterations that can cause liver injury. Acetaldehyde, for example, has multiple toxic effects on liver cells and liver function. Age and sex play a role in metabolism of alcohol and production of harmful metabolites. The ADH system is depressed by testosterone. Thus, women tend to produce greater amounts of acetaldehyde and are more predisposed to alcohol-induced liver damage than men.29 Age also appears to affect the alcohol-metabolizing abilities of the liver and the resistance to hepatotoxic effects. Furthermore, genetic factors may influence the severity of alcohol-induced liver disease.

Alcohol-Induced Liver Disease

About 2 million people in the United States are suspected of having alcoholic liver disease, and 14,000 die each year of cirrhosis.30 Most deaths from alcoholic cirrhosis are attributable to liver failure, bleeding esophageal varices, or kidney failure. It has been estimated that there are 14 million alcoholics in the United States. Only approximately 10% to 15% of alcoholics develop cirrhosis, however, suggesting that other conditions such as genetic and environmental factors contribute to its occurrence.3

The spectrum of alcoholic liver disease includes fatty liver disease, alcoholic hepatitis, and cirrhosis.3,4 Fatty liver disease is characterized by the accumulation of fat in hepatocytes, a condition called steatosis (Fig. 30-10). The liver becomes yellow and enlarges owing to 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 an excess amount of alcohol, even though adequate carbohydrates, fats, and proteins were included in the diet.31 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. Alcoholic hepatitis is characterized by inflammation and necrosis of liver cells.3,4,32 The cardinal sign of alcoholic hepatitis is rapid onset of jaundice. Other manifestations include fever, hepatic tenderness, pain, anorexia, nausea, ascites, and liver failure. Persons with severe hepatic hepatitis may have encephalopathy. The condition is always serious and sometimes fatal. The immediate prognosis correlates with severity of liver cell injury. In some cases, the disease progresses rapidly to liver failure and death. The mortality rate in the acute stage is about 10%.4 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.

Alcoholic cirrhosis is the end result of repeated bouts of drinking-related hepatocyte injury and regeneration and designates the onset of end-stage alcoholic liver disease. The gross appearance of the early cirrhotic liver is one of fine, uniform nodules on its surface (Fig. 30-11A). The condition has traditionally been called micronodular or Laennec cirrhosis. Initially, the developing fibrous septa extend through the sinusoids from the central to the portal regions and the entrapped hepatocytes generate uniform micronodules (Fig 30-11B). With more advanced cirrhosis, regenerative processes cause the nodules to become larger and more irregular in size and shape. As this occurs, the nodules cause the liver to become relobulized through the formation of new portal tracts and venous outflow channels. The nodules may compress the hepatic veins, curtailing blood flow out of the liver and producing portal hypertension, extrahepatic portosystemic shunts, and cholestasis.

Nonalcoholic Fatty Liver Disease

The term nonalcoholic fatty liver disease (NAFLD) is often used to describe fatty liver disease with the potential for progression to cirrhosis and end-stage liver disease arising from causes other than alcohol.33-35 The condition can range from simple steatosis (fatty infiltration of the liver)
to nonalcoholic steatohepatitis (steatosis with inflammation and hepatocyte necrosis). Although steatosis alone does not appear to be progressive, approximately 20% of persons with nonalcoholic steatohepatitis progress to cirrhosis over the course of a decade. Obesity, type 2 diabetes, the metabolic syndrome, and hyperlipidemia are coexisting conditions frequently associated with fatty liver disease (see Chapter 33). The condition is also associated with other nutritional abnormalities, surgical conditions, drugs, and occupational exposure to toxins. Both rapid weight loss and parenteral nutrition may lead to NAFLD.

The pathogenesis of NAFLD is thought to involve both lipid accumulation within hepatocytes and formation of free radicals, in a manner similar to that which occurs with alcohol metabolism. The primary metabolic abnormalities leading to lipid accumulation are poorly understood but are thought to include alterations in the pathways for uptake, synthesis, degradation, or secretion of hepatic lipids resulting from insulin resistance. Obesity increases the synthesis and reduces the oxidation of free fatty acids. Type 2 diabetes or insulin resistance also increases adipose tissue lipolysis and the subsequent production of free fatty acids. When the capacity of the liver to export triglyceride is exceeded, excess fatty acids contribute to the development of steatosis and fatty liver disease. Both ketones and free fatty acids are inducers of previously described CYP P450 enzymes of the MEOS pathway, which results in free radical formation, including hydrogen peroxide and superoxide. Abnormal lipid peroxidation ensues, followed by direct hepatocyte injury, release of toxic byproducts, inflammation, and fibrosis.

NAFLD is usually asymptomatic, although fatigue and discomfort in the right upper quadrant of the abdomen may be present. Mildly to moderately elevated serum levels of AST, ALT, or both are the most common and often the only abnormal laboratory findings. Other abnormalities, including hypoalbuminemia, a prolonged prothrombin time, and hyperbilirubinemia, may be present in persons with cirrhotic-stage liver disease. The diagnosis of NAFLD requires liver biopsy and exclusion of alcohol as a cause of the disorder.

The aim of treatment is to slow progression of NAFLD and to prevent liver-related illness. Both weight loss and exercise improve insulin resistance and are recommended in conjunction with treatment of associated metabolic disturbances. Alcohol use should be avoided. Disease progression is slow and the magnitude of disease-related morbidity and mortality is uncertain. Liver transplantation is an alternative for some persons with end-stage liver disease, but NAFLD may recur or develop after liver transplantation.

Hepatic Syndromes

As with other organ systems, the liver responds to a number of injurious insults with similar cellular and tissue responses, including hepatocyte degeneration, necrosis and apoptosis, and fibrosis. Clinically, these changes commonly lead to a few syndromes including cirrhosis, portal hypertension, and liver failure.

Cirrhosis

Cirrhosis represents the end stage of chronic liver diseases in which much of the functional liver tissue has been replaced by fibrous tissue. Although cirrhosis usually is associated with alcoholism, it can develop in the course of other disorders, including viral hepatitis, nonalcoholic liver disease, and biliary disease. 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 disease (i.e., copper deposition).
Cirrhosis is characterized by diffuse fibrosis and conversion of normal liver architecture into nodules containing proliferating hepatocytes encircled by fibrosis. The formation of nodules, which vary in size from very small (<3 mm, micronodules) to large (several centimeters, macronodules), represents a balance between regenerative activity and constrictive scarring. The fibrous tissue that replaces normally functioning liver tissue 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; obstruction of biliary channels and exposure to the destructive effects of bile stasis; and loss of liver cells, leading to liver failure.

The manifestations of cirrhosis are variable, ranging from asymptomatic hepatomegaly to hepatic failure (Fig. 30-12). 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 complain of constipation. Hepatomegaly and jaundice also are common signs of cirrhosis. There may be abdominal pain because of liver enlargement or stretching of the liver’s fibrous tissue capsule. This pain is located in the epigastric area or in the upper right quadrant and is described as dull, aching, and causing a sensation of fullness.

The late manifestations of cirrhosis are related to portal hypertension and liver cell failure. Splenomegaly, ascites, and portosystemic shunts (i.e., esophageal varices, hemorrhoids, and caput medusae) result from portal hypertension. Other complications include bleeding due to decreased clotting factors, thrombocytopenia due to splenomegaly, gynecomastia and a feminizing pattern of pubic hair distribution in men because of testicular atrophy, spider angiomas, 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 increase in portal venous pressure. Normally, 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 (see Fig. 30-2). Portal hypertension can be caused by a variety of conditions that increase resistance to hepatic blood flow, including prehepatic, posthepatic, and intrahepatic obstructions. Prehepatic causes of portal hypertension include obstructive thrombosis, narrowing of the portal vein before it enters the liver, and massive splenomegaly with increased splenic blood flow. The main posthepatic causes are right-sided heart failure and hepatic vein outflow obstruction. The dominant intrahepatic cause of portal hypertension is cirrhosis, in which bands of fibrous tissue and fibrous nodules distort the architecture of the liver and increase the resistance to blood flow.

**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 in the portal vein 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.
The major clinical consequences of portal hypertension arise from the increased pressure and dilation of the venous channels behind the obstruction. In addition, collateral channels open that connect the portal circulation with the systemic venous circulation. The complications of the increased portal vein pressure and the opening of collateral channels are ascites, congestive splenomegaly, and the formation of portosystemic shunts with bleeding from esophageal varices (Fig. 30-13).

**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. Ascites usually becomes clinically evident when at least 500 mL of fluid has accumulated. However, the amount may be so great (frequently several liters) that it not only distends the abdomen, but also interferes with breathing. The fluid is generally serous, having less than 3 g of protein (largely albumin) and a concentration of solutes (glucose, sodium, and potassium) similar to that in the blood.

Although the mechanisms responsible for the development of ascites are not completely understood, several factors appear to contribute to fluid accumulation, including an increase in hydrostatic pressure due to portal hypertension, salt and water retention by the kidney, and decreased colloidal osmotic pressure due to impaired synthesis of albumin by the liver. Diminished blood volume (i.e., underfill theory) and excessive blood volume (i.e., overfill theory) have been used to explain the increased salt and water retention by the kidney. According to the underfill theory, a contraction in the effective blood volume causes the kidney to retain salt and water. The effective blood volume may be reduced because of loss of fluid into the peritoneal cavity or because of vasodilation caused by the presence of circulating vasodilating substances. The overfill theory proposes that the initial event in the development of ascites is renal retention of salt and water caused by disturbances in the liver itself. These disturbances include failure of the liver to metabolize aldosterone, causing an increase in salt and water retention by the kidney. Another likely contributing factor in the pathogenesis of ascites is a decreased colloidal osmotic pressure, which limits reabsorption of fluid from the peritoneal cavity (see Chapter 8).

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. Two classes of diuretics are used: a diuretic that acts in the distal part of the nephron to inhibit aldosterone-dependent sodium reabsorption and a loop diuretic such as furosemide (see Chapter 24). Oral potassium supplements often are given to prevent hypokalemia. Large-volume paracentesis (removal of 5 L or more of ascitic fluid) may be done in persons with massive ascites and pulmonary compromise. Because the removal of fluid produces a decrease in vascular volume along with increased plasma renin activity and aldosterone-mediated sodium and water reabsorption by the kidneys, a volume expander such as albumin usually is administered to maintain the effective circulating volume. A transjugular intrahepatic portosystemic shunt may be inserted in persons with refractory ascites (to be discussed).

**Spontaneous bacterial peritonitis** is a potential complication in persons with both cirrhosis and ascites. The infection is serious and carries a high mortality rate even when treated with antibiotics. Presumably, the peritoneal fluid is seeded with bacteria from the blood or lymph or from passage of bacteria through the bowel wall. Symptoms include fever and abdominal pain. Other symptoms include worsening of hepatic encephalopathy, diarrhea, hypothermia, and shock. It is diagnosed by a neutrophil count of 250/mm³ or higher and a protein concentration of 1 g/dL or less in the ascitic fluid.

**Splenomegaly.** The spleen enlarges progressively in portal hypertension because of shunting of blood into the splenic vein. The enlarged spleen often gives rise to sequestration of significant numbers of blood elements.
and development of a syndrome known as hyper-splenism. Hypersplenism is characterized by a decrease in the life span of all the formed elements of the blood and a subsequent decrease in their numbers, leading to anemia, thrombocytopenia, and leukopenia. The decreased life span of the blood elements is thought to result from an increased rate of removal because of the prolonged transit time through the enlarged spleen.

**Portosystemic Shunts and Esophageal Varices.** 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.3,4 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. 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 esophagus3,4,39,41 (Fig. 30-14). 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) due to splenomegaly may further complicate the control of esophageal bleeding.

Treatment of portal hypertension and esophageal varices is directed at prevention of initial hemorrhage, management of acute hemorrhage, and prevention of recurrent hemorrhage. Pharmacologic therapy is used to lower portal venous pressure and prevent initial hemorrhage. Nonselective β-adrenergic blocking drugs (propranolol, nadolol) commonly are used for this purpose.39 These agents reduce portal venous pressure by decreasing splanchnic blood flow and thereby decreasing blood flow in collateral channels.

Several methods are used to control acute hemorrhage, including pharmacologic therapy, balloon tamponade, and emergent endoscopic therapy.39,41 Pharmacologic methods include the administration of octreotide, a long-acting synthetic analog of somatostatin. Somatostatin, which is normally produced by enteric cells in the gastrointestinal tract, by delta cells in the endocrine pancreas, and from the hypothalamus, reduces splanchnic and hepatic blood flow and portal pressures in persons with cirrhosis. The drug, which is given intravenously, provides control of variceal bleeding in up to 80% of cases.41 Balloon tamponade provides compression of the varices and is accomplished through the insertion of a tube with inflatable gastric and esophageal balloons. After the tube has been inserted, the balloons are inflated; the esophageal balloon compresses the bleeding esophageal veins, and the gastric balloon helps to maintain the position of the tube. Emergent endoscopic procedures include sclerotherapy, in which the varices are injected with a sclerosing solution that obliterates the vessel lumen, and ligation, in which a band is inserted around the bleeding vessel.

Prevention of recurrent hemorrhage focuses on lowering portal venous pressure and diverting blood flow away from the easily ruptured collateral channels.39 Two procedures may be used for this purpose: the surgical creation of a portosystemic shunt or a transjugular intrahepatic portosystemic shunt (TIPS). *Surgical portosystemic shunt* procedures involve the creation of an opening between the portal vein and a systemic vein. These shunts have a considerable complication rate, and TIPS has evolved as the preferred treatment for refractory portal hypertension. The TIPS procedure involves insertion of an expandable metal stent between a branch of the hepatic vein and the portal vein using a catheter inserted through the internal jugular vein. A limitation of the procedure is that stenosis and thrombosis of the stent occur in most cases over time, with consequent risk of rebleeding. A complication that is associated with the creation of a portosystemic shunt is hepatic encephalopathy, which is thought to result when ammonia and other neurotoxic substances from the gut pass directly into the systemic circulation without going through the liver.

**Liver Failure**

The most severe clinical consequence of liver disease is hepatic failure.3,4 It may result from sudden and massive
liver destruction, as in fulminant hepatitis, or be the result of progressive damage to the liver, as occurs in alcoholic cirrhosis. Whatever the cause, 80% to 90% of hepatic functional capacity must be lost before hepatic failure occurs. In many cases, the progressive decompensating effects of the disease are hastened by intercurrent conditions such as gastrointestinal bleeding, systemic infection, electrolyte disturbances, or superimposed diseases such as heart failure.

**Manifestations.** The manifestations of liver failure reflect the various synthesis, storage, metabolic, and elimination functions of the liver (Fig. 30-15). *Fetor hepaticus* refers to a characteristic musty, sweetish odor of the breath in the patient in advanced liver failure, resulting from the metabolic by-products of the intestinal bacteria.

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 blood 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. Thrombocytopenia often occurs as the result of splenomegaly. The person with liver failure 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.

*Endocrine disorders,* particularly disturbances in gonadal (sex hormone) 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.

Liver failure also 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.

The *hepatorenal syndrome* refers to a functional 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_ refers to the totality of central nervous system manifestations of liver failure.\(^3,4\) 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 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 person 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 from there to the cerebral circulation. Hepatic encephalopathy may become worse after a large protein meal or gastrointestinal tract bleeding. Narcotics and tranquilizers are poorly metabolized by the liver, and administration of these drugs may contribute to central nervous system depression and precipitate hepatic encephalopathy.

A nonabsorbable antibiotic, such as neomycin, may be given to eradicate bacteria from the bowel and thus prevent this cause of ammonia production. Another drug that may be used is lactulose. It is not absorbed from the small intestine but moves directly to the large intestine, where it is broken down by colonic bacteria to small organic acids that cause production of large, loose stools with a low pH. The low pH favors the conversion of ammonia to ammonium ions, which are not absorbed by the blood. The acid pH also inhibits the intestinal degradation of amino acids, proteins, and blood.

**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.

Liver transplantation rapidly is becoming a realistic form of treatment for many persons with irreversible chronic liver disease, fulminant liver failure, primary biliary cirrhosis, chronic active hepatitis, sclerosing cholangitis, and certain metabolic disorders that result in end-stage liver disease. Currently, 1-year survival rates approach 90%, and a 3-year survival rate of 80% is achieved at many transplantation centers in the United States.\(^4\) In addition to longer survival, many liver recipients are now experiencing improved quality of life, including return to active employment. Unfortunately, the shortage of donor organs severely limits the number of transplantations that are done, and many persons die each year while waiting for a transplant. During the past several years a number of innovative methods have been developed to deal with the shortage, including split liver transplantation, in which a cadaver liver is split into two pieces and transplanted into two recipients, and living donor transplantation, in which a segment or lobe from the liver from a living donor is resected and grafted into a recipient.\(^4\)

**Cancer of the Liver**

**Primary Liver Cancers**

There are two major types of primary liver cancer: hepatocellular carcinoma, which arises from the liver cells, and cholangiocarcinoma, which is a primary cancer of bile duct cells.\(^3,4\) Although primary tumors of the liver are relatively rare in developed countries of the world, the liver shares with the lung the distinction of being the most common site of metastatic tumors.

**Hepatocellular Carcinoma.** Hepatocellular cancer, the most common form of liver cancer, is the fifth most common cancer and third leading cause of cancer-related mortality worldwide.\(^4,46\) In East Asia and sub-Saharan Africa, the incidence is 15 cases per 100,000. In Europe, Australia, and the United States, the incidence is approximately 3 cases per 100,000.\(^4,46\) There has been an increased incidence, however, in developed countries as a consequence of chronic HCV infection.\(^4,46\)

Among the factors identified as etiologic agents in liver cancer are chronic viral hepatitis (i.e., HBV, HCV, HDV), chronic alcoholism, nonalcoholic fatty liver disease, long-term exposure to environmental agents such as aflatoxin, and drinking water contaminated with arsenic. Just how these etiologic agents contribute to the development of liver cancer is still unclear. 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.\(^3,46\) They are activated by hepatocytes and their products incorporated into the host DNA with the potential for developing 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 preexisting cirrhosis. Usually, the liver is enlarged when these symptoms appear. Various paraneoplastic syndromes (e.g., disturbances due to ectopic hormone or growth factor production by the tumor [see Chapter 7]) have been associated with hepatocellular cancer, including erythrocytosis (erythropoietin), hypoglycemia (insulin-like growth factor), and hypercalcemia (parathyroid-related protein). Serum α-fetoprotein, which is present during fetal life but barely detectable in the serum after the age of 2 years, is present in 50% of persons with hepatocellular carcinoma. However, the test lacks specificity and is not very useful as a surveillance or diagnostic tool. Diagnostic methods include ultrasonography, CT scans, and MRI. Liver biopsy may be used to confirm the diagnosis.

Primary cancers of the liver are often far advanced at the time of diagnosis. 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.

**Cholangiocarcinoma.** Cholangiocarcinoma is a malignancy of the biliary tree, arising from bile ducts within and outside the liver. It accounts for 7.6% of cancer deaths worldwide and 3% of cancer deaths in the United States. 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 long-standing 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.

**Metastatic Tumors**

Metastatic tumors of the liver are much more common than primary tumors. Common sources include colorectal cancer and those spread from breast, lung, or urogenital cancer. 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 infections, autoimmune disorders, toxic injury, metabolic diseases, 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 infections have the potential for progression to the carrier state, chronic hepatitis, and hepatocellular carcinoma. Autoimmune hepatitis involves the immune destruction of hepatocytes. 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.

As the major drug-metabolizing and detoxifying organ in the body, the liver is subject to potential damage from an enormous array of pharmaceutical and environmental chemicals. Drugs and chemicals can exert their effects by causing hepatocyte injury and death or by cholestatic liver damage due to injury of biliary drainage structures. Drug reactions can be predictable based on the drug’s chemical structure and metabolites, or unpredictable (idiosyncratic) based on individual characteristics of the person receiving the drug. Early identification of drug-induced liver disease is important because withdrawal of the drug is curative in most cases. 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.

Portal hypertension, cirrhosis, and liver failure represent clinical syndromes common to a number of liver diseases. 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. 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 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. 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.

There are two types of primary cancers of the liver: hepatocellular (the most common form, derived from hepatocytes and their precursors) and cholangiocarcinoma (bile duct cancer, arising from biliary epithelium). Hepatocellular carcinoma, which is associated with HBV
and HCV infection, alcoholic cirrhosis, and food contaminants (e.g., aflatoxins), is the fifth most common cancer and third leading cause of cancer-related mortality worldwide. Cholangiocarcinoma occurs primarily in older persons with a history of chronic disorders of the bile ducts. Although primary tumors of the liver are relatively rare in developed countries of the world, the liver shares with the lung the distinction of being the most common site of metastatic tumors.