CHAPTER 20

Digestive System Disorders

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, the student is expected to:

1. Describe the various causes of vomiting and the vomiting process.
2. Differentiate diarrhea from constipation.
3. Differentiate cleft lip from cleft palate.
4. Describe the common oral infections and periodontal disease.
5. Explain the common causes of dysphagia.

DISORDERS OF THE LIVER AND PANCREAS

GALLBLADDER DISORDERS

The gallbladder and biliary tract are frequently affected by one or more interrelated problems involving the formation of gallstones (Fig. 20-15). At least 10% of the population has gallstones and 500,000 surgical procedures are done per year in the United States to treat gallbladder disease.

- *Cholelithiasis* refers to formation of gallstones, which are masses of solid material or **calculi** that form in the bile.
- *Cholecystitis* refers to inflammation of the gallbladder and cystic duct.
- *Cholangitis* is inflammation usually related to infection of the bile ducts.
- *Choledocholithiasis* pertains to obstruction by gallstones of the biliary tract.

Pathophysiology

Gallstones vary in size and shape and may form initially in the bile ducts, gallbladder, or cystic duct. They may consist primarily of cholesterol or bile pigment (bilirubin) or may be of mixed content, including calcium salts (Fig. 20-16). The content of the stone depends on the primary factor predisposing to calculus formation. Cholesterol stones appear white or crystalline, whereas bilirubin stones are black.

Small stones may be "silent" and excreted in the bile, whereas larger stones are likely to obstruct the flow of bile in the cystic or common bile ducts, causing pain. Note the comparative size of the stones and the bile ducts (see Fig. 20-16).

Gallstones tend to form when the bile contains a high concentration of a component such as cholesterol or there is a deficit of bile salts. Inflammation or infection in the biliary structures may provide a focus for stone formation or may alter the solubility of the constituents, fostering the development of a calculus. Whether inflammation or infection is primary or secondary to stone formation is not always clear. Once a focus or nucleus

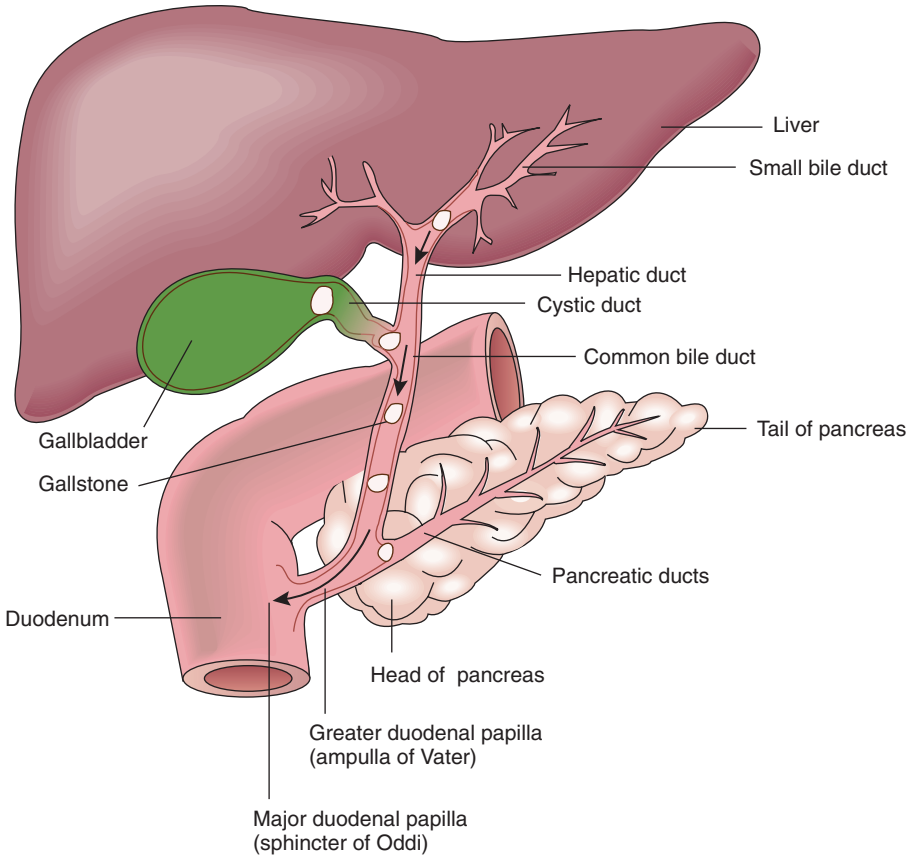


FIGURE 20-15 The biliary ducts and pancreas with possible locations of gallstones.

FIGURE 20-16 Examples of gallstones with the gallbladder. Compare the size of the stones to the bile duct. *Upper left*, Black bilirubin stones. *Upper right*, Clear or white cholesterol stones. *Lower*, Mixed stones. *(Courtesy of Paul Emmerson and Seneca College of Applied Arts and Technology, Toronto, Ontario, Canada.)*

forms, the stone tends to grow, as additional solutes are deposited on it, particularly if bile flow is sluggish.

The presence of gallstones may cause irritation and inflammation in the gallbladder wall (cholecystitis), and this susceptible tissue may then be infected. Infecting organisms are usually *Escherichia coli* or enterococci, which gain access to the gallbladder through the sphincter of Oddi or from the portal veins or adjacent lymph nodes.

When a stone obstructs bile flow in the cystic or common bile duct, biliary colic develops, consisting of severe spasms of pain resulting from strong muscle contractions attempting to move the stone along. Obstruction of the biliary system at the sphincter of Oddi may also cause pancreatitis because the pancreatic secretions are backed up or bile refluxes into the pancreatic ducts.

Etiology

Cholesterol gallstones occur twice as often in women as men. They tend to develop in individuals with high cholesterol levels in the bile. Factors that indicate a high risk for gallstones include obesity, high cholesterol intake, **multiparity** (several children), and the use of oral contraceptives or estrogen supplements. Bile pigment stones are more common in individuals with hemolytic anemia, alcoholic cirrhosis, or biliary tract infection.

Signs and symptoms

Gallstones are frequently asymptomatic. However, larger calculi may obstruct a duct at any time, causing sudden severe waves of pain (biliary colic) in the upper right quadrant of the abdomen or epigastric area, often radiating to the back and right shoulder. Nausea and vomiting are usually present. The pain increases for some time and then may decrease if the stone moves on. If the pain continues, and jaundice develops as the bile backs up into the liver and blood, surgical intervention may be necessary. There is also a risk of a ruptured gallbladder if obstruction persists. Acute cholecystitis is usually associated with some degree of obstruction and inflammation. Severe pain is often precipitated by eating a fatty meal; fever, leukocytosis, and vomiting accompany the pain.

Chronic cholecystitis is manifested by milder signs, although the course may be punctuated by acute episodes. Signs often include intolerance to fatty foods, excessive belching, bloating, and mild epigastric discomfort.

Treatment

The gallbladder and gallstones may be removed using laparoscopic surgery. In many cases, the stones are fragmented by such methods as extracorporeal shock wave lithotripsy (using high-energy sound waves), sometimes assisted by administration of bile acids or drugs to break down the stone.

THINK ABOUT 20-8

a. Differentiate cholelithiasis from choledocholithiasis.
b. Explain three factors predisposing to cholesterol gallstones.
c. Describe how a cholesterol stone forms.

JAUNDICE

Jaundice (**icterus**) refers to the yellowish color of the skin and other tissues that results from high levels of bilirubin in the blood. The color is usually apparent first in the sclera, or white area of the eye. Bilirubin is a product of the hemolysis of red blood cells (RBCs) and the breakdown of hemoglobin (see Fig. 17-4).

Jaundice or **hyperbilirubinemia** is not itself a disease but rather is a sign of many different types of primary disorders. These disorders are classified in three groups (Fig. 20-17):

1. *Prehepatic* jaundice results from excessive destruction of red blood cells and is characteristic of hemolytic anemias or transfusion reactions. Liver function is normal but is unable to handle the additional bilirubin. *Physiologic jaundice of the newborn* is common 2 to 3 days after birth. Increased hemolysis of red blood cells combined with the immature infant liver leads to a transient mild hyperbilirubinemia.
2. *Intrahepatic* jaundice occurs in individuals with liver disease, such as hepatitis or cirrhosis. It is related to impaired uptake of bilirubin from the blood and

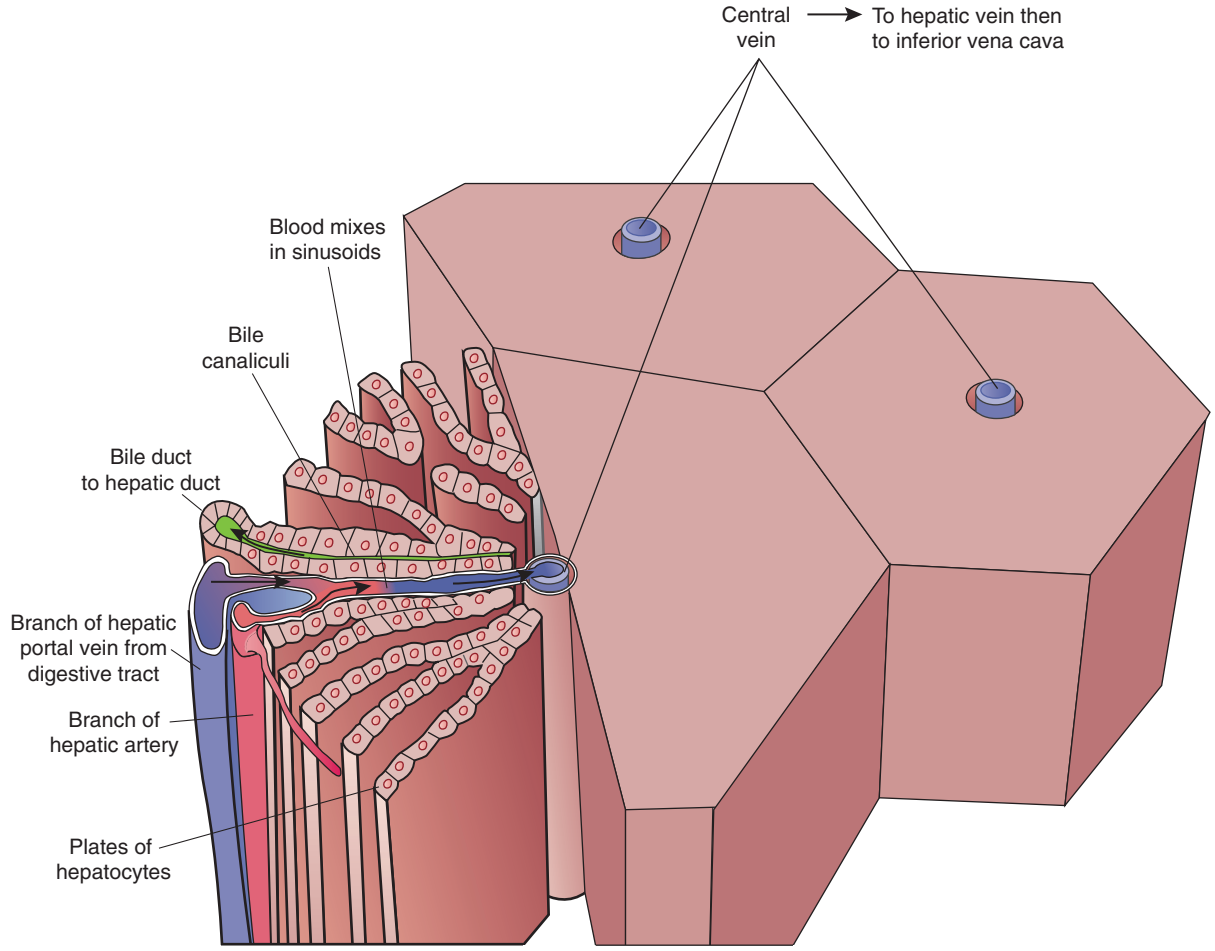


FIGURE 20-17 Structure of liver lobule.

decreased conjugation of bilirubin by the hepatocytes (Fig. 20-18).

3. *Posthepatic* jaundice is caused by obstruction of bile flow into the gallbladder or duodenum and subsequent backup of bile into the blood. Congenital atresia of the bile ducts, obstruction caused by cholelithiasis, inflammation of the liver, or tumors all result in posthepatic jaundice.

The type of jaundice present in an individual may be indicated by increases in the serum bilirubin level and changes in the stools (see Fig. 20-17). For example, serum levels of unconjugated bilirubin (indirect-reacting) are elevated in prehepatic jaundice, whereas posthepatic jaundice results from increased amounts of conjugated bilirubin (direct) in the blood. In patients with liver disease, both intrahepatic and posthepatic jaundice may be present because inflammation or infection both impairs hepatocyte function and obstructs the bile canaliculi, leading to elevations in the blood of both unconjugated and conjugated bilirubin. In persons with posthepatic jaundice, the obstruction prevents bile from entering the intestine, interfering with digestion and resulting in a light-colored stool. Also, the bile salts that enter the blood and tissues as bile backs up cause irritation and **pruritus** (itching) of the skin. Treatment depends on removing the cause. Phototherapy is effective in mild forms, whereby exposure to ultraviolet light promotes the conjugation of bilirubin.

HEPATITIS

Hepatitis refers to inflammation of the liver. It may be idiopathic (fatty liver) or result from a local infection (viral hepatitis), from an infection elsewhere in the body (e.g., infectious mononucleosis or amebiasis), or from chemical or drug toxicity. Mild inflammation impairs hepatocyte function, whereas more severe inflammation and necrosis may lead to obstruction of blood and bile flow in the liver and impaired liver cell function. Given the many functions of the liver, damage to the liver cells has extensive effects in the body. Fortunately, the liver has a good functional reserve and excellent regenerative powers.

Viral Hepatitis

Pathophysiology

Although a number of viruses may affect the liver cells, hepatitis is considered to result from infection by a group of viruses that specifically target the hepato-

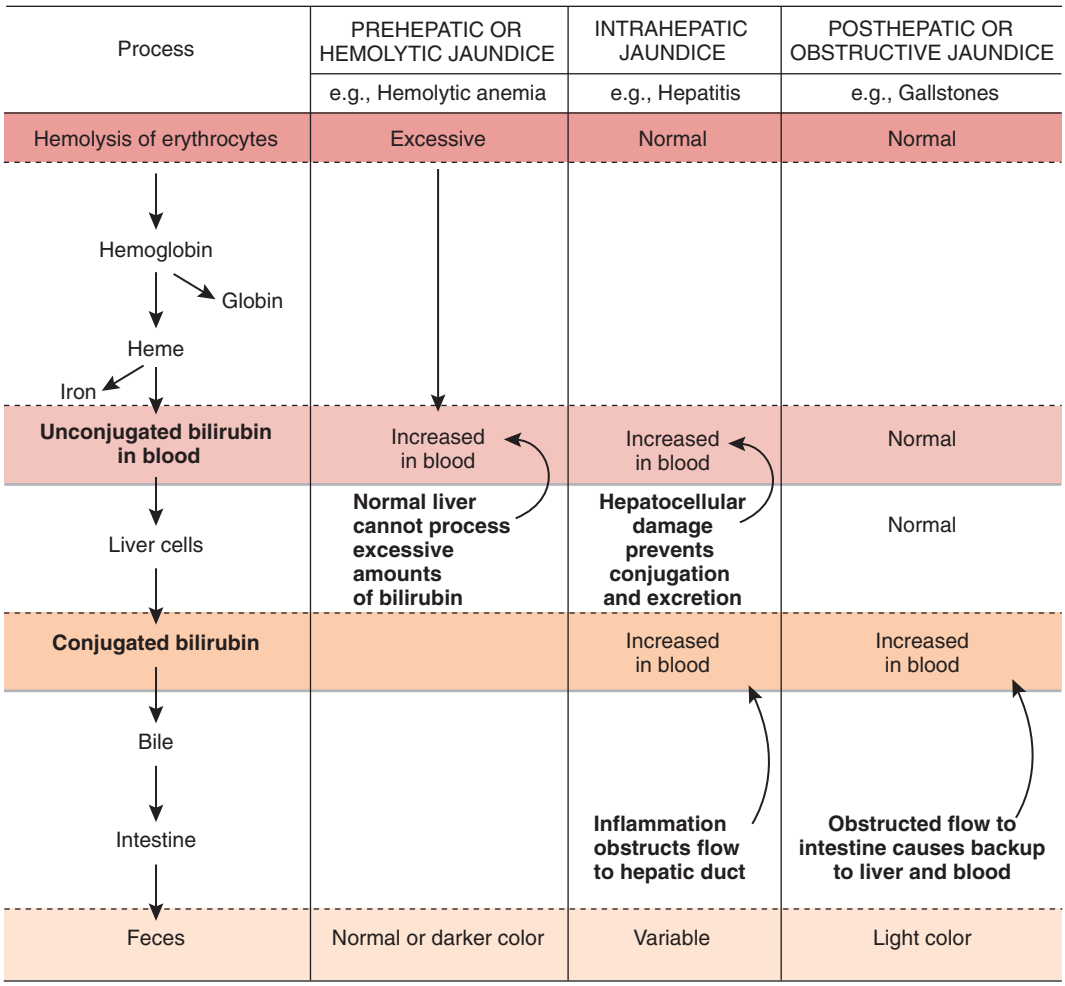


FIGURE 20-18 Types of jaundice.

cytes. These include hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV). There are other viruses causing hepatitis that have not yet been fully identified, meanwhile they have been temporarily designated F and G or non A-E hepatitis virus.

The liver cells are damaged in two ways—by direct action of the virus (e.g., hepatitis C) or cell-mediated immune responses to the virus (e.g., hepatitis B). Cell injury results in inflammation and necrosis in the liver. Both the hepatocytes and the liver appear swollen, and diffuse necrosis may be present. With severe inflammation, biliary stasis may develop, leading to backup of bile into the blood.

The degree of inflammation and damage varies. Many cases are mild and are not identified. Some cases show a few manifestations but not jaundice; in other cases fulminant hepatitis develops with massive necrosis and liver failure. Depending on the severity of the inflammation, the hepatic cells may regenerate, or fibrous scar tissue may form in the liver. Scar tissue often obstructs the channels used for blood and bile flow, interfering with the unique organization of the liver lobule, and leading to further damage from ischemia.

Chronic inflammation occurs with hepatitis B, C, and D and is defined as persistent inflammation and necrosis of the liver for more than 6 months. This type of disease eventually causes permanent liver damage (fibrosis) and cirrhosis. There is also an increased incidence of hepatocellular cancer associated with chronic hepatitis.

Hepatitis B, C, and D may exist in a carrier state, in which asymptomatic individuals carry the virus in their hepatocytes but can transmit the infection via their blood or body fluids to others. Carriers may be individuals who have never had active disease or have a chronic low-grade infection.

Etiology

The viruses causing hepatitis vary in their characteristics, mode of transmission, incubation time, and effects. These are summarized in Table 20-5.

Hepatitis A. Also called *infectious hepatitis,* hepatitis A is caused by a small RNA virus called the hepatitis

TABLE 20-5 Types of Hepatitis

Disease	Agent	Transmission	Incubation Period	Serum Markers	Carrier/ Chronic
Hepatitis A (infectious)	HAV (RNA virus)	Oral-fecal	2-6 wk	anti-HAV IgM anti-HAV IgG	None
Hepatitis B (serum)	HBV (DNA double-strand virus)	Blood and body fluids	1-6 mo (average, 60-90 days)	HBsAg anti-HBs HBcAb IgM HBcAb IgG HBeAg, HBeAb	Carrier and chronic
Hepatitis C	HCV (RNA virus)	Blood and body fluids	2 wk-6 mo (average, 6-9 wk)	anti-HCV	Carrier and chronic
Hepatitis D, chronic (delta)	HDV (defective RNA virus requires presence of HBV)	Blood and body fluids	2-10 wk	anti-HDV IgM anti-HDV IgG	Chronic
Hepatitis E	HEV (RNA virus)	Oral-fecal contamination	2-9 wk	HE Ag	None
Toxic Hepatitis	Hepatotoxins; chemicals or drugs	Direct exposure	Days to months	N/A	Acute or chronic
Chronic Non-infectious Hepatitis	Autoimmune, metabolic, idiopathic	N/A	N/A	Various autoantibodies	Chronic

N/A, not applicable

A virus, or HAV. It is transmitted primarily by the oral-fecal route, often from contaminated water or shellfish. Outbreaks may occur in daycare centers. Sexual transmission has occurred in the homosexual population. HAV has a relatively short incubation period of 2 to 6 weeks. HAV causes an acute but self-limiting infection and does not have a carrier or chronic state.

Fecal shedding of the virus (the contagious period) begins several weeks before the onset of signs (Fig. 20-19*A*). At this time, the first antibodies, IgM-HAV, appear, followed shortly by the second group of antibodies, IgG-HAV, which remain in the serum for years, providing immunity against further infection. A vaccine is available for those who are traveling to an endemic area or anyone with any liver disease; this vaccine is administered to both children and adults. Gamma globulin provides temporary protection and may be administered to those just exposed to HAV.

Hepatitis B. In 2006 the CDC received reports of 4758 new cases in the United States, but estimate the occurrence rate is ten times that number, with many cases being asymptomatic. Further, there are more than 1 million carriers in the country, and 4000 to 5000 deaths annually from associated cirrhosis and cancer. Over 50% of those who test HIV-positive are also positive for Hepatitis B. Global estimates are over 2 billion with 350 million of those being carriers. Unfortunately, 50% of cases are asymptomatic, facilitating transmission to others.

Formerly called *serum hepatitis*, this form of hepatitis is caused by the hepatitis B virus (HBV), a partially double-stranded DNA virus. The whole virion is often called a Dane particle. This virus is more complex and consists of three antigens—two core antigens (HBcAg and HBeAg) and one surface antigen (HBsAg). Each antigen stimulates antibody production in the body (see Fig. 20-19). These serum antigens and antibodies are useful in diagnosing and monitoring the course of hepatitis, including the development of chronic hepatitis. For example, large amounts of HBsAg are produced by infected liver cells early in the course of the infection. When this antigen persists in the serum, it poses a high risk of continued active infection and damage to the liver (chronic disease). A carrier state is also common for HBV, in which the individual is asymptomatic but is contagious for the disease.

Hepatitis B has a relatively long incubation period, averaging about 2 months. Long incubation periods make it more difficult to track sources and contacts for infections. A "window," or prolonged lag time, occurs before the serum markers or symptoms become present,

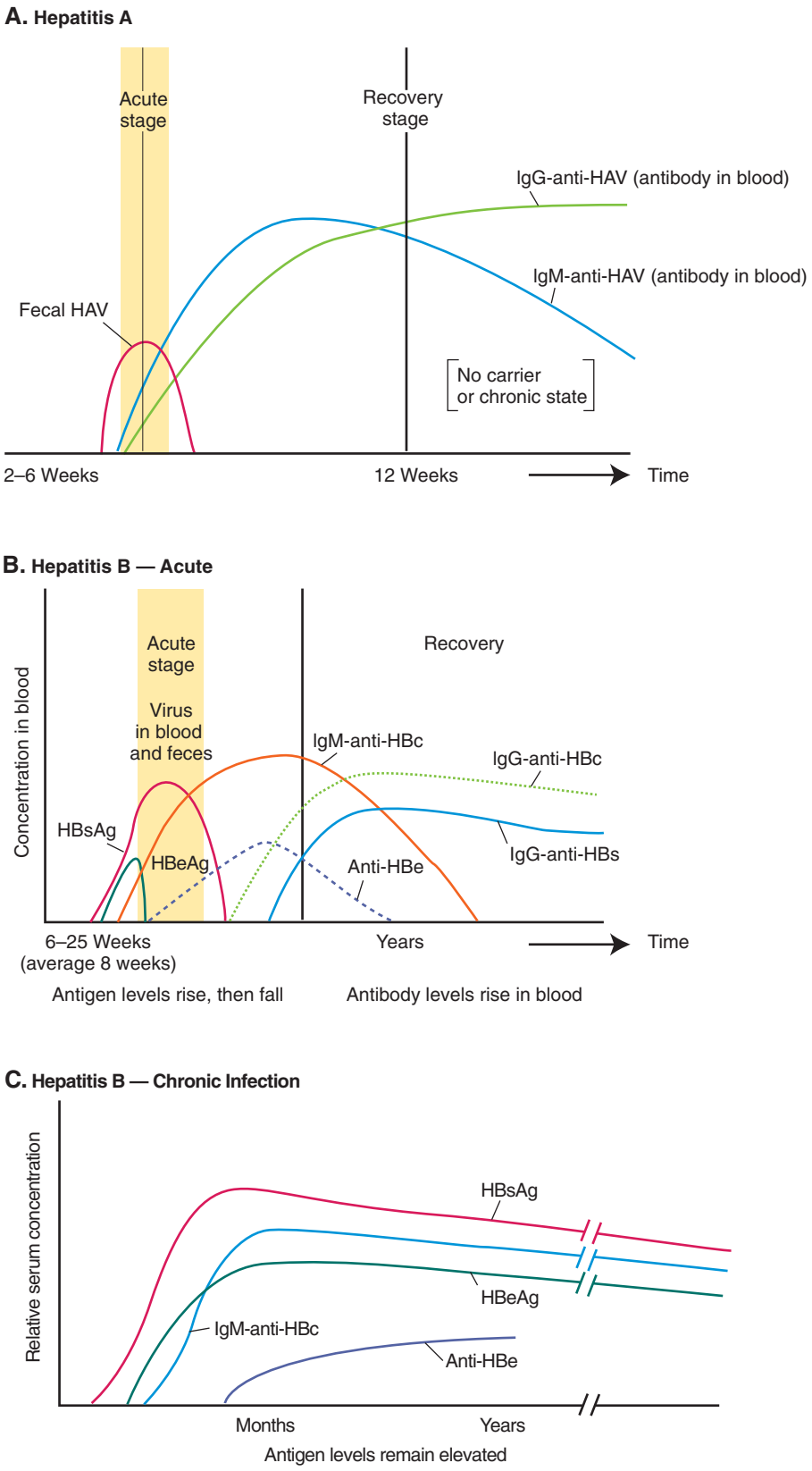


FIGURE 20-19 Serologic changes seen with hepatitis.

during which time the virus cannot be detected but can be transmitted to others.

HBV infection is transmitted primarily by infected blood but is found in many body secretions. Blood transfusions are currently processed to reduce the risk of transmission. Intravenous drug abusers have a high incidence of HBV infection. Hemodialysis increases the risk, as does exposure to blood or body fluids in health care workers if barrier precautions are not taken. Sexual transmission has been noted, and HBV can be passed to the fetus during pregnancy. Activities such as tattooing and body piercing may transmit the virus. An HBV vaccine is available for long-term protection for those in high-risk groups, including health professionals, and is now routinely administered to children. HBV immune globulin is available as a temporary measure.

Hepatitis C. Formerly called non-A-non-B (or NANB) hepatitis, hepatitis C is the most common type of hepatitis transmitted by blood transfusions. The virus is a single-stranded RNA virus. Approximately half the cases enter a chronic disease state. WHO estimates that there are 130 to 170 million people infected globally, and the CDC estimates the prevalence rate in the United States to be 3.2 million cases. HCV infection increases the risk of hepatocellular carcinoma. This form of hepatitis may exist in a carrier state.

Hepatitis D. The agent for hepatitis D is also called delta virus. This incomplete RNA virus requires the presence of hepatitis B virus (HBsAg) to replicate and produce active infection. HDV infection usually increases the severity of HBV infection. HDV is also transmitted by blood; there is a high incidence of infection in intravenous drug abusers.

Hepatitis E. Hepatitis E is caused by HEV, a single-stranded RNA virus, and is spread by the oral-fecal route. It is similar to HAV and lacks a chronic or carrier state. It is more common in countries in Asia and Africa, where it causes a fulminant hepatitis that produces a high mortality rate in pregnant women.

RESEARCH 20-1

Discuss the method of naming the hepatitis viruses, both known and those currently under investigation, given their differences and commonalities.

Signs and symptoms

The manifestations of acute hepatitis vary from mild or asymptomatic to severe disease that is often rapidly fatal. The course of hepatitis has three stages: first, the preicteric or prodromal stage; next, the icteric or jaundice stage; and last, the posticteric or recovery stage (Fig. 20-20).

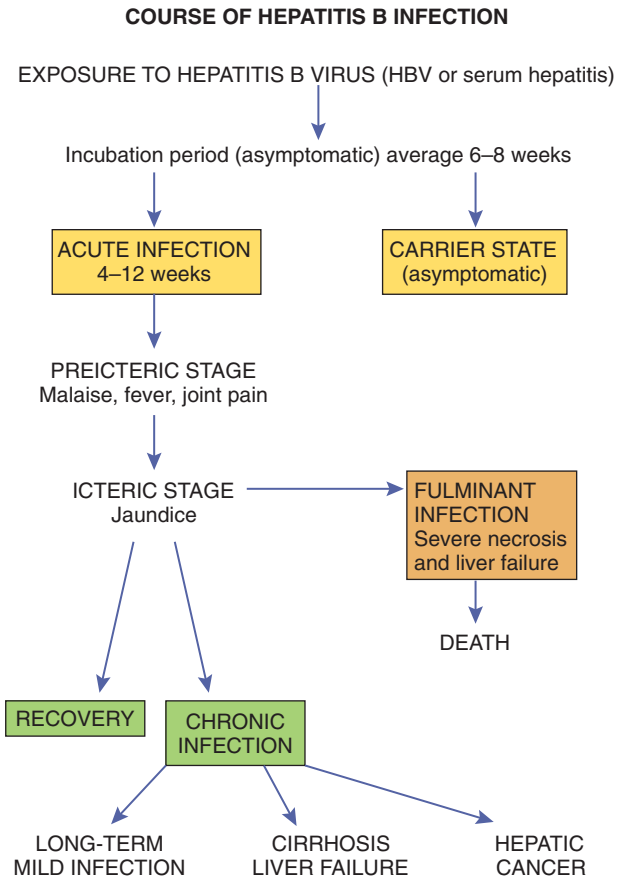


FIGURE 20-20 The course of hepatitis B infection.

1. Onset of the *preicteric* stage may be insidious, with fatigue and malaise, anorexia and nausea, and general muscle aching. Sometimes fever, headache, a distaste for cigarettes, and mild upper right quadrant discomfort are present. Serum levels of liver enzymes (e.g., aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) are elevated.
2. The *icteric* stage marks the onset of jaundice as serum bilirubin levels rise. As biliary obstruction increases, the stools become light in color, the urine becomes darker, and skin becomes pruritic. The liver is tender and enlarged (hepatomegaly), causing a mild aching pain. In severe cases, blood clotting times may be prolonged, because the synthesis of blood clotting factors is impaired. This stage tends to last longer in patients with hepatitis B.
3. The *posticteric* or recovery stage is marked by a reduction in signs, although this period may extend over some weeks. On average, the acute stage of hepatitis A lasts 8 to 10 weeks, whereas hepatitis B is prolonged over 16 weeks.

Treatment

There is no method of destroying hepatitis viruses in the body at this time. Gamma globulin, if available, may be helpful when given early in the course. Supportive

measures such as rest and a diet high in protein, carbohydrate, and vitamins are most useful.

Chronic hepatitis B and C may be treated with interferon α and lamivudine (Epivir or 3TC) to decrease viral replication, although this treatment is effective in only 30% to 40% of individuals. A combination of slow-acting interferon and the antiviral drug, Ribavirin, have reduced the rate of viral replication in 80% of HCV patients. Otherwise, gradual destruction of the liver occurs, leading to cirrhosis or hepatocellular cancer.

Toxic or Nonviral Hepatitis

A variety of **hepatotoxins,** such as chemicals or drugs, may cause inflammation and necrosis in the liver. These reactions may be direct effects of the toxins or an immune response (hypersensitivity) to certain materials. Toxic effects may result from sudden exposure to large amounts of a substance or from long-term exposure, perhaps in the workplace. Hepatotoxic drugs include acetaminophen, halothane, phenothiazines, and tetracycline. Toxic chemicals include solvents such as carbon tetrachloride, toluene, or ethanol. Reye's syndrome, which occurs when aspirin is used in the presence of viral infections, also causes toxic effects on the liver. Hepatocellular damage can result from either of two processes, inflammation with necrosis, or **cholestasis** (obstructed flow of bile). The signs of toxicity are similar to those of infectious hepatitis. The toxic chemical must be removed from the body as quickly as possible to reduce the risk of permanent liver damage.

THINK ABOUT 20-9

a. Explain how prehepatic jaundice might develop and the expected change in serum bilirubin.
b. Describe two ways in which hepatitis A differs from hepatitis B.
c. Describe how serum markers may indicate the presence of chronic viral hepatitis.
d. Explain why the individual who is a carrier for HBV is considered a threat to public health.

CIRRHOSIS

Cirrhosis is a disorder in which there is progressive destruction of liver tissue leading eventually to liver failure when 80% to 90% of the liver has been destroyed. It is the end result of a number of chronic liver diseases. About 28,000 persons die each year in the United States, 50% of which are alcohol related.

Cirrhosis may be classified by the structural changes that take place (e.g., micronodular or macronodular) or the cause of the disorder. In some cases, cirrhosis may be linked to specific underlying disorders, particularly congenital problems or inherited metabolic disorders. The four general categories of cirrhosis based on cause are:

1. Alcoholic liver disease (the largest group, also called portal or Laënnec's cirrhosis)
2. Biliary cirrhosis, associated with immune disorders and those causing obstruction of bile flow, for example, stones or cystic fibrosis, in which mucous plugs form in the bile ducts
3. Postnecrotic cirrhosis, linked with chronic hepatitis or long-term exposure to toxic materials
4. Metabolic, usually caused by storage disorders such as hemochromatosis

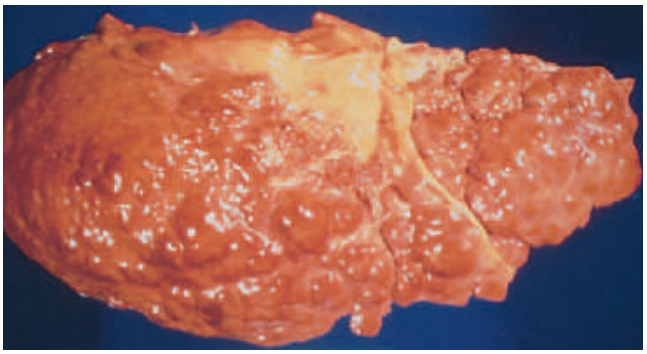


FIGURE 20-21 Cirrhosis resulting from chronic viral hepatitis. Note the broad scar and nodular surface. *(From Kumar V, Abbas AK, Fausto M:* Robbins and Cotran Pathologic Basis of Disease, *7th ed. Philadelphia, WB Saunders, 2005.)*

Pathophysiology

Cirrhosis is a disorder in which the liver demonstrates extensive diffuse fibrosis and loss of lobular organization (see Fig. 20-17). Nodules of regenerated hepatocytes may be present but are not necessarily functional because the vascular network and biliary ducts are distorted (Fig. 20-21). Even if the primary cause is removed, further damage is likely because fibrosis interferes with the blood supply to liver tissues or the bile may back up, leading to ongoing inflammation and damage. Initially the liver is enlarged, but it becomes small and shrunken as fibrosis proceeds. In many cases degenerative changes are asymptomatic until the disease is well advanced.

Liver biopsy and serologic tests may determine the cause and extent of the damage. The progressive changes that occur in biliary and postnecrotic cirrhosis are directly linked to inflammation, necrosis, and fibrosis associated with the primary condition.

In patients with *alcoholic liver disease,* or portal cirrhosis, there are several stages in the development of hepatocellular damage related to the effects of alcohol. Alcohol and its metabolites, such as acetaldehyde, are toxic to the liver cells and alter many metabolic processes in the liver. Secondary malnutrition may aggravate the damaging effects on liver cells.

TABLE 20-6 Common Manifestations of Liver Disease with Rationale

Signs or Symptoms	Pathophysiology
Fatigue, anorexia, indigestion, weight loss	Metabolic dysfunction in the liver, such as decreased gluconeogenesis; decreased bile for digestion and absorption; portal hypertension, leading to edema of intestinal wall and interfering with digestion and absorption
Ascites	Portal hypertension, elevated aldosterone and ADH levels, decreased serum albumin level, lymphatic obstruction in liver
General edema	Elevated aldosterone and ADH levels, decreased serum albumin level
Esophageal varices, hemorrhoids	Portal hypertension and collateral circulation
Splenomegaly	Portal hypertension
Anemia	Decreased absorption and storage of iron and vitamin B_{12}, malabsorption, splenomegaly, bleeding
Leukopenia, thrombocytopenia	Splenomegaly, possible bone marrow depression by amonia and other toxins
Increased bleeding, purpura	Decreased absorption of vitamin K, decreased production of clotting factors by liver, thrombocytopenia
Hepatic encephalopathy, tremors, confusion, coma	Metabolic dysfunction with inability to remove ammonia from protein metabolism and other toxic substances
Gynecomastia, impotence, irregular menses	Impaired inactivation of sex hormones (e.g., estrogen) leads to imbalance
Jaundice	Impaired extraction and conjugation of bilirubin; decreased production of bile and obstruction of bile flow
Pruritus	Bile salts in the tissues resulting from biliary obstruction

ADH, antidiuretic hormone.

1. The initial change in alcoholic liver disease is the accumulation of fat in liver cells, causing *fatty liver.* Other than enlargement of the liver or hepatomegaly, this stage is asymptomatic and is reversible if alcohol intake is reduced.
2. In the second stage, *alcoholic hepatitis,* inflammation and cell necrosis occur. Fibrous tissue forms, an irreversible change. Acute inflammation may develop when alcohol intake increases or binge drinking becomes more excessive. This second stage may also be asymptomatic, or it may manifest with mild symptoms, such as anorexia, nausea, and liver tenderness. In some patients, after an episode of excessive alcohol intake, there may be sufficient damage to precipitate liver failure, encephalopathy, and death.
3. The third stage, or *end-stage cirrhosis,* is reached when fibrotic tissue replaces normal tissue, significantly altering the basic liver structure to the extent that little normal function remains. Signs of portal hypertension or impaired digestion and absorption are the usual early indicators of this stage.

The pathophysiologic effects of cirrhosis evolve from two factors: the loss of liver cell functions and interference with blood and bile flow in the liver.

Major functional losses in persons with cirrhosis include:

- Decreased removal and conjugation of bilirubin
- Decreased production of bile
- Impaired digestion and absorption of nutrients, particularly fats and fat-soluble vitamins
- Decreased production of blood clotting factors (prothrombin, fibrinogen) and plasma proteins (albumin)
- Impaired glucose/glycogen metabolism
- Inadequate storage of iron and vitamin B_{12}
- Decreased inactivation of hormones, such as aldosterone and estrogen
- Decreased removal of toxic substances, such as ammonia and drugs

These changes are linked with clinical signs in Table 20-6.

Altered blood chemistry, including abnormal levels of electrolytes or amino acids, and excessive ammonia or other toxic chemicals affect the central nervous system, leading to *hepatic encephalopathy.* Serum ammonia levels correlate well with the clinical signs of encephalopathy. Ammonia is an end product of protein metabolism in the liver or intestine, and then is converted by liver cells into urea for excretion by the kidneys. The ingestion of a meal high in protein or an episode of bleeding in the digestive tract may cause a marked elevation in serum ammonia concentration and may precipitate severe encephalopathy.

The second group of effects is related to obstruction of bile ducts and blood flow by fibrous tissue as follows:

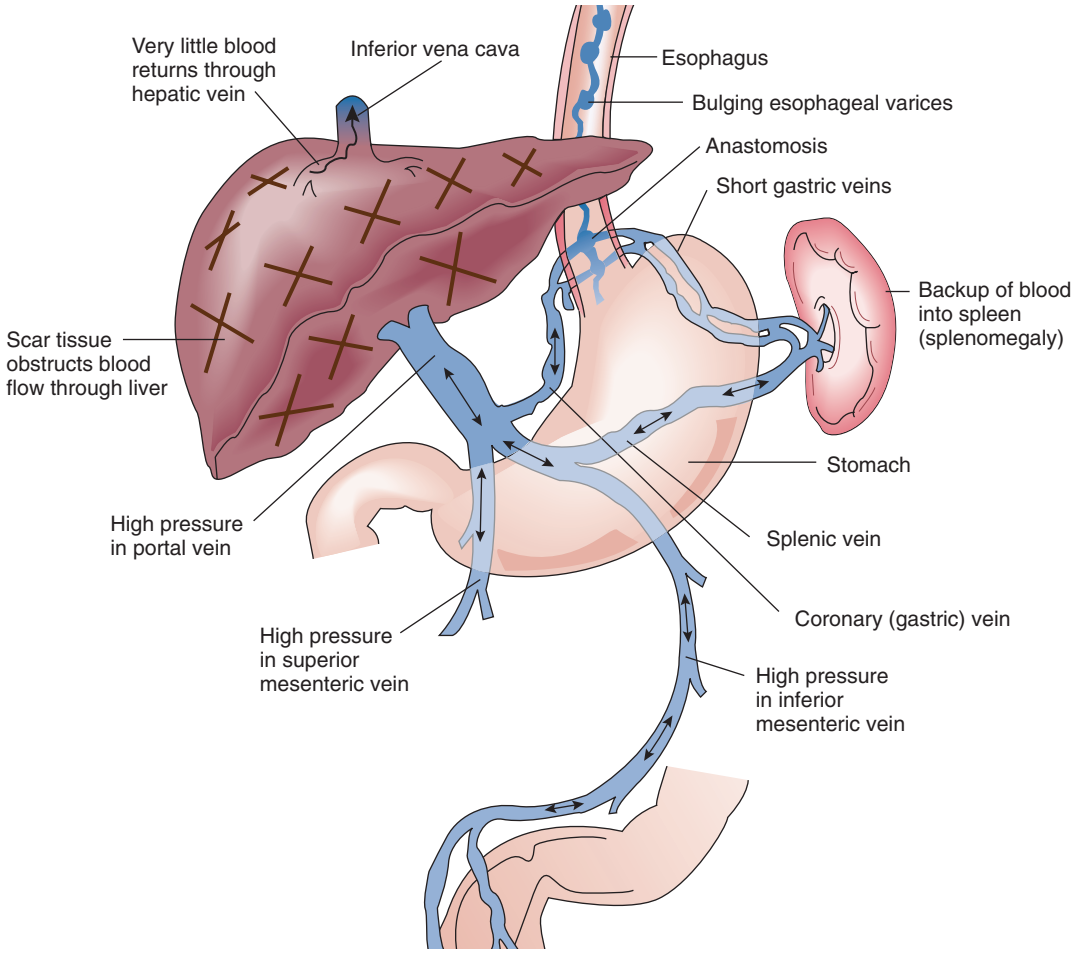


FIGURE 20-22 Development of esophageal varices.

- Reduction of the amount of bile entering the intestine, impairing digestion and absorption
- Backup of bile in the liver, leading to obstructive *jaundice* with elevated conjugated and unconjugated bilirubin levels in the blood
- Blockage of blood flow through the liver, leading to high pressure in the portal veins, or *portal hypertension* (Fig. 20-22)
- Congestion in the spleen (**splenomegaly**), increasing hemolysis
- Congestion in intestinal walls and stomach, impairing digestion and absorption
- Development of esophageal varices
- Development of ascites, an accumulation of fluid in the peritoneal cavity that causes abdominal distention and pressure

Because the esophageal veins have several points of anastomosis, or collateral channels to join with the gastric veins, the increased pressure of blood extends into the esophageal veins, creating large distended and distorted veins (varicose veins or varices) near the mucosal surface of the esophagus. These veins are easily torn by food passing down the esophagus. Hemorrhage of these *esophageal varices* is a common complication of cirrhosis (Fig. 20-23).

The high pressure in the portal veins and lymphatics, in conjunction with other factors, also affects fluid shifts in the hepatic portal system, leading to *ascites* (Fig. 20-24). Portal hypertension increases the hydrostatic pressure in the veins and lymphatics; the increased serum aldosterone levels result in increased sodium ion and water in the extracellular compartment; and the decreased serum levels of albumin lower the plasma osmotic pressure. All these factors contribute to a shift of fluid out of the blood and into the peritoneal cavity.

Signs and symptoms

Initial manifestations of cirrhosis are often mild and vague and include such signs as fatigue, anorexia, weight loss, anemia, and diarrhea. Dull aching pain may be present in the upper right quadrant of the abdomen.

As cirrhosis advances, ascites and peripheral edema develop, increased bruising is evident, esophageal varices form, and eventually jaundice and encephalopathy occur (see Table 20-6). An imbalance in sex hormone levels secondary to impaired inactivation mechanisms

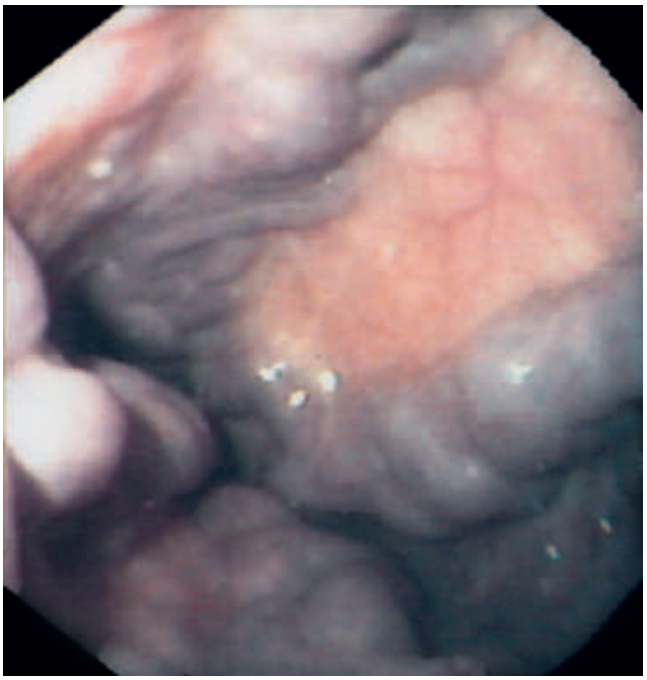


FIGURE 20-23 Esophageal varices: endoscopic view. *(From Gitlin N, Strauss RM:* Atlas of Clinical Hepatology. *Philadelphia, WB Saunders, 1995.)*

leads to spider nevi on the skin, testicular atrophy, impotence, gynecomastia, and irregular menses. Complications involve ruptured esophageal varices, leading to hemorrhage, circulatory shock, and acute hepatic encephalopathy.

Acute encephalopathy manifests as asterixis, a "hand-flapping" tremor, and confusion, disorientation, convulsions, and coma. Chronic encephalopathy is characterized by personality changes, memory lapses, irritability, and disinterest in personal care.

Another complication of cirrhosis is the presence of frequent infections, often respiratory or skin infections. These infections are encouraged by excessive fluids in the tissues that interfere with the diffusion of nutrients and thus lead to delayed tissue regeneration and healing. Also, decreased protein availability in the body and anemia impair tissue maintenance. Pruritus causes scratching of the skin that may damage the skin barrier, leading to infection.

A summary of the effects of cirrhosis and liver failure is illustrated in Figure 20-25.

Treatment

Supportive or symptomatic treatment, such as avoiding fatigue and exposure to infection, is necessary.

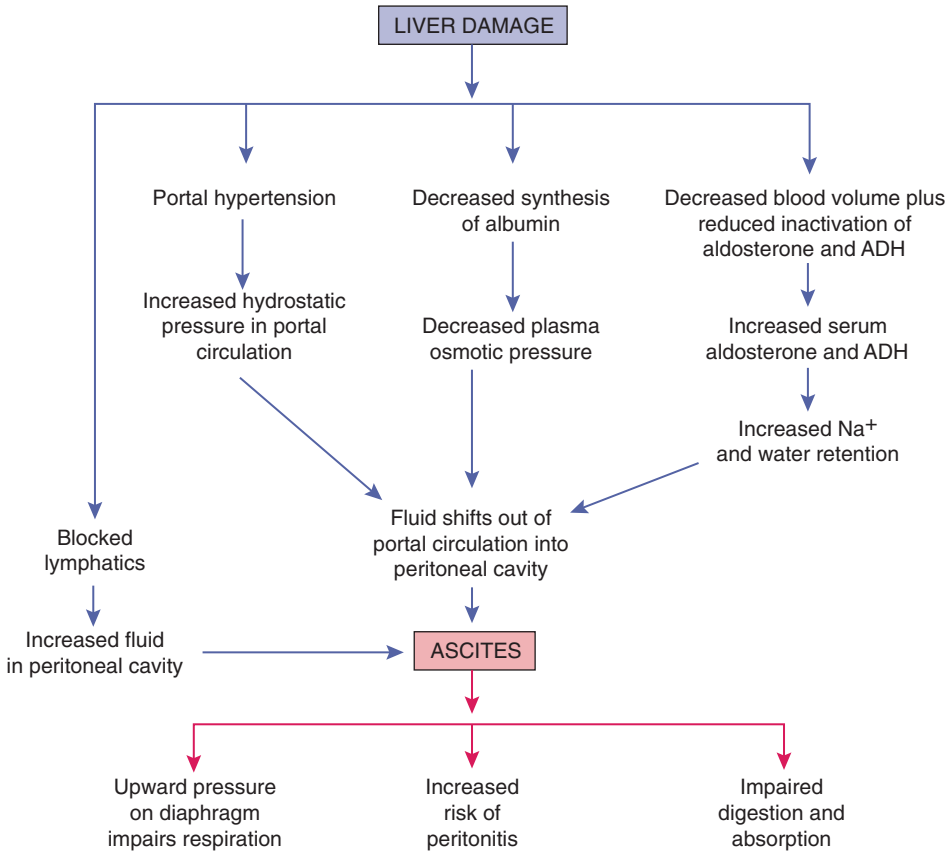


FIGURE 20-24 Development of ascites with cirrhosis.

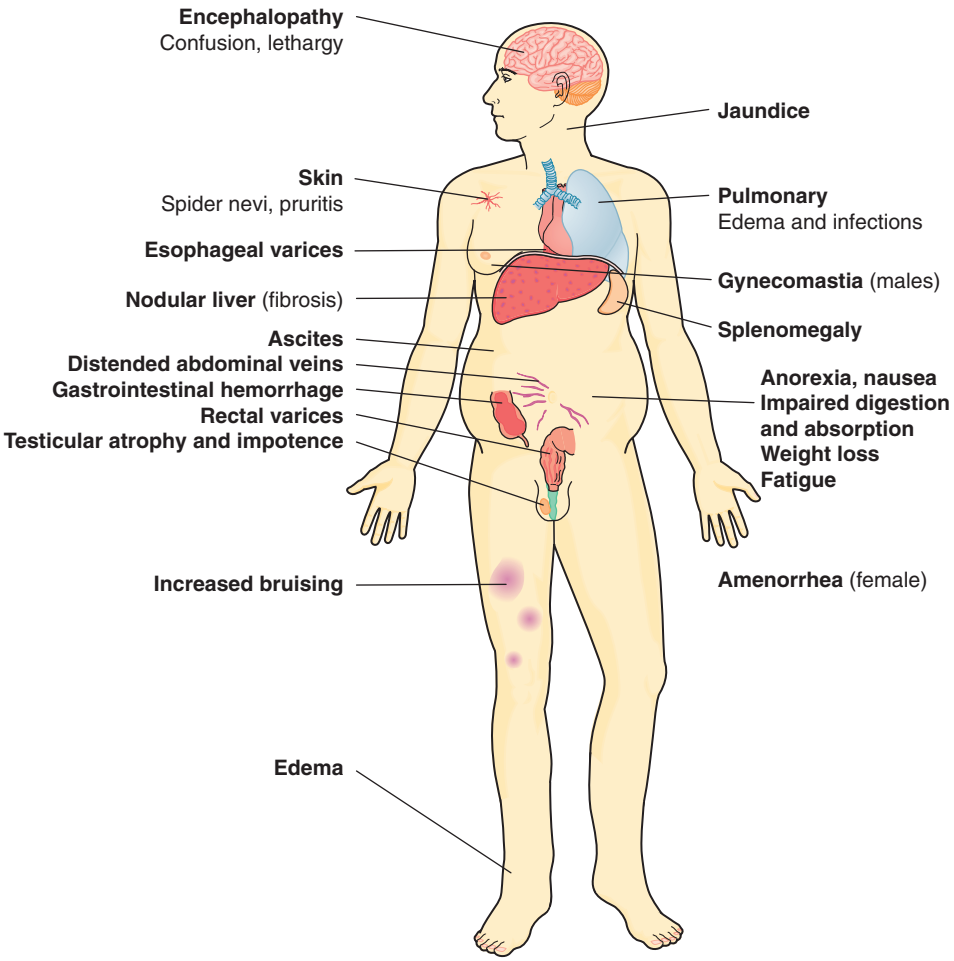


FIGURE 20-25 Effects of advanced cirrhosis.

Dietary restrictions include restrictions on protein and sodium intake. High carbohydrate intake and vitamin supplements are necessary.

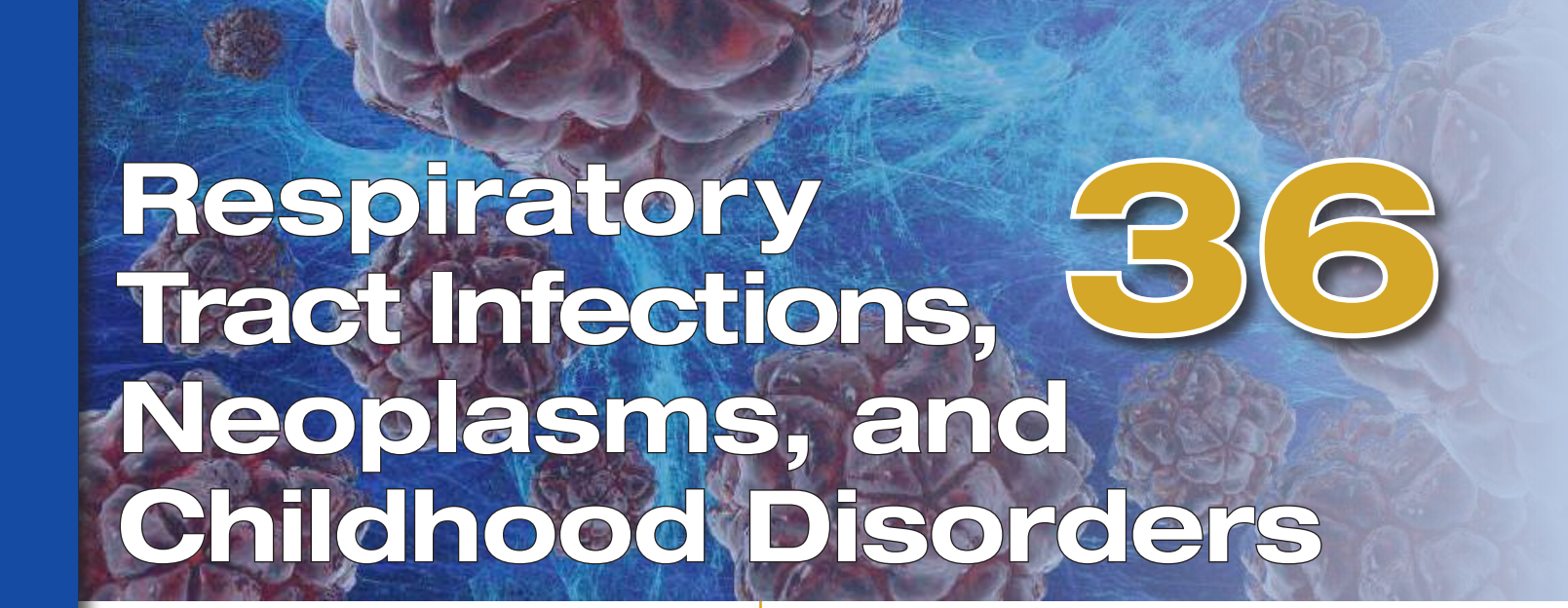
Serum electrolytes may have to be balanced, possibly requiring the use of diuretics (e.g., furosemide) to reduce body fluids. Paracentesis to remove excess fluid may be necessary, followed by albumin transfusions to prevent third spacing of fluid. Antibiotics such as neomycin are useful to reduce intestinal flora and control serum ammonia levels. Ruptured esophageal varices need emergency treatment. Portocaval shunts may be used to reduce portal hypertension.

Liver transplants provide another option (see Chapter 3). Many tests are required before transplant to determine the tissue match and general health status. Transplanting part of the liver from a suitable living donor (LDLT) has become more common because the wait time is less than that for a cadaver donor (about 18,000 persons await liver transplant, only 5000 cadaver organs will likely be available). The liver tissue is able to grow in both donor and recipient providing a complete functional organ for both. This process was first used successfully in children, in whom size of the transplant is an issue, and now is being used in adults. It is riskier in adults because more donor tissue (half the liver) is required. Currently living donor liver transplant is the standard practice in pediatric transplants and adult to adult transplants are being done in all major transplant centers in the United States.

LIVER CANCER

Although secondary tumors are very common in the liver, primary malignant tumors are relatively rare, making up less than 2% of all cancers. However the number of cases and deaths are climbing for unknown reasons. The American Cancer Society has predicted 22,620 new cases and 18,160 deaths in the United States in 2009. There has not been a significant decrease in either incidence or mortality rates for liver cancer.

The most common primary tumor is hepatocellular carcinoma, developing in cirrhotic livers (Fig. 20-26). Cirrhosis may be secondary to metabolic disorders or hepatitis. Tumors may also result from prolonged exposure to carcinogenic chemicals. Secondary or metastatic cancer often arises from areas served by the hepatic



36 Respiratory Tract Infections, Neoplasms, and Childhood Disorders

Sheila Grossman

Respiratory illnesses represent one of the more common reasons for visits to the physician, admission to the hospital, and forced inactivity among all age groups. The common cold, although not usually serious, is a frequent cause of missed work and school days. Pneumonia is the sixth leading cause of death in the United States, particularly among the elderly and those with compromised immune function.[1] In addition, it is the first cause of death among children in the world.[2] Tuberculosis remains one of the deadliest diseases in the world and affects one third of the world population.[3] A large number of people have multidrug-resistant TB, and many are immunocompromised. Immunocompromised people experience all types of bacterial, viral, and fungal infections. The most frequently seen fungal infections include histoplasmosis, coccidioidomycosis, and blastomycosis. Lung cancer remains the leading cause of cancer death worldwide.[4] Children with upper and lower airway infections represent a large number of visits to primary care providers. Premature infants, especially those who experience respiratory distress syndrome (RDS), are at high risk for chronic respiratory infections and other complications such as bronchopulmonary dysplasia.

RESPIRATORY TRACT INFECTIONS

After completing this section of the chapter, you should be able to meet the following objectives:

- Characterize community-acquired pneumonia, hospital-acquired pneumonia, and pneumonia in immunocompromised people in terms of pathogens, manifestations, and prognosis.
- Describe the immunologic properties of the tubercle bacillus, and differentiate between primary tuberculosis and reactivated tuberculosis on the basis of their pathophysiology.

The respiratory tract is susceptible to infectious processes caused by multiple types of microorganisms. Infections can involve the upper respiratory tract (*i.e.,* nose, oropharynx, and larynx), the lower respiratory tract (*i.e.,* lower airways and lungs), or the upper and lower airways. For the most part, the signs and symptoms of respiratory tract infections depend on the function of the structure involved, the severity of the infectious process, and the person's age and general health status. The discussion in this section of the chapter focuses on the common cold, rhinosinusitis, influenza, pneumonia, tuberculosis, and fungal infections of the lung. Acute respiratory infections in children are discussed in the last section of the chapter.

Viruses are the most frequent cause of respiratory tract infections. They can cause infections ranging from a self-limited cold to life-threatening pneumonia. Moreover, viral infections can damage bronchial epithelium, obstruct airways, and lead to secondary bacterial infections. Each viral species has its own pattern of respiratory tract involvement. For example, the rhinoviruses grow best at 33°C to 35°C and remain strictly confined to the upper respiratory tract.[5] Viruses are able to move from the nasal cavity to the upper airways by binding to the intercellular adhesion molecule (ICAM-1). People with compromised immunological response are most susceptible to having a virus cause serious gas exchange or ventilation problems.[6]

Other microorganisms, such as bacteria (*e.g.,* pneumococci, staphylococci), mycobacteria (*e.g., Mycobacterium tuberculosis*), fungi (*e.g., Histoplasma capsulatum* [histoplasmosis], *Coccidioides immitis* [coccidioidomycosis], and *Blastomyces dermatitidis* [blastomycosis]), and opportunistic organisms (*e.g., Pneumocystis jirovecii*), also produce infections of the lung. In turn, many of these infections produce significant morbidity and mortality.

The Common Cold

The common cold is a viral infection of the upper respiratory tract. It occurs more frequently than any other respiratory tract infection. Most adults have two to three colds per year, whereas the average school child may have up to 6 to 8 per year.[6]

Etiology and Pathogenesis

Initially thought to be caused by either a single "cold virus" or a group of them, the common cold is now recognized to be associated with a number of viruses.[6] The rhinoviruses are the most common cause of colds. Other viral causes include parainfluenza viruses, respiratory syncytial virus (RSV), human metapneumovirus (hMPV), coronaviruses, and adenoviruses. In children a new virus, bocavirus, causes respiratory tract infections. The season of the year and the person's age, immunological state, and prior exposure are important factors in identifying the type of virus causing the infection and the type of symptoms that occur. For example, outbreaks of colds due to rhinoviruses are most common in early fall and late spring. Colds due to RSV peak in the winter and spring months, and infections due to the adenoviruses and coronaviruses are more frequent during the winter and spring months. Infections resulting from the RSV and parainfluenza viruses are most common and severe in children younger than 3 years of age. Infections occur less frequently and with milder symptoms with increasing age until after 65 years of age. Parainfluenza viruses often produce lower respiratory symptoms with first infections, but less severe upper respiratory symptoms with reinfections.

The "cold viruses" are spread rapidly from person to person. Children are the major reservoir of cold viruses, often acquiring a new virus from another child in school or day care. The fingers are the greatest source of spread, and the nasal mucosa and conjunctival surface of the eyes are the most common portals for entry of the virus. The most highly contagious period is during the first 3 days after the onset of symptoms, and the incubation period is approximately 5 days.[7] Aerosol spread of colds through coughing and sneezing is much less important than the spread through direct mucous membrane contact by fingers picking up the virus from contaminated surfaces and carrying it to the nasal membranes and eyes.[7,8]

Clinical Manifestations

The condition usually begins with a feeling of dryness and stuffiness affecting mainly the nasopharynx. This is followed by excessive production of nasal secretions and tearing of the eyes, which is often referred to as rhinitis. Usually, the secretions remain clear and watery. The mucous membranes of the upper respiratory tract become reddened and swollen. Often there is postnasal dripping (PND), which irritates the pharynx and larynx, causing sore throat and hoarseness. The affected person may experience headache and generalized malaise. In severe cases, there may be chills, fever, and exhaustion. The disease process is usually self-limited and lasts approximately 5 to 6 days.[6,7] However, respiratory viruses account for approximately 40% to 75% of cases of acute otitis media in children.

Treatment

The common cold is an acute and self-limited illness in people who are otherwise healthy. Therefore, symptomatic treatment with rest and antipyretic drugs is usually all that is needed. Antibiotics are ineffective against viral infections and are not recommended. Many over-the-counter (OTC) remedies are available for treating the common cold. Antihistamines are popular OTC drugs because of their action in drying nasal secretions. However, they may dry up bronchial secretions and worsen the cough, and they may cause dizziness, drowsiness, and impaired judgment. If these drugs are used too frequently over too many days, they can cause rebound symptoms. In addition, there is no evidence that they shorten the duration of the cold. Decongestant drugs (*i.e.,* sympathomimetic agents) are available in OTC nasal sprays, drops, and oral cold medications. These drugs constrict the blood vessels in the swollen nasal mucosa and reduce nasal swelling. Rebound nasal swelling can occur with indiscriminate use of nasal drops and sprays. Oral preparations containing decongestants may cause systemic vasoconstriction and elevation of blood pressure when given in doses large enough to relieve nasal congestion. Thus, people with hypertension, heart disease, hyperthyroidism, diabetes mellitus, or other health problems should avoid taking these drugs.[6]

There is controversy regarding the use of vitamin C to reduce the incidence and severity of colds and influenza. Some studies have found vitamin C intake to be beneficial, and others have found it to be of questionable value in decreasing the severity of a common cold.[8]

Rhinosinusitis

Rhinitis refers to inflammation of the nasal passages and sinusitis as inflammation of the paranasal sinuses. Although it has not been universally accepted, the suggestion has been made that the term *rhinosinusitis* is a more accurate term for what is commonly referred to as *sinusitis*. This is based on two key facts: the mucosa of the nasal cavities and paranasal sinuses are lined with a continuous mucous membrane layer, and viral upper respiratory tract infections frequently precede or occur along with sinus infections.[7]

The paranasal sinuses are air sacs that develop during embryogenesis from a series of ridges and furrows within the cartilaginous capsule surrounding the developing nasal cavity. As development progresses, outpouchings from these furrows become lined with ciliated respiratory epithelium and invade the surrounding facial bones to become the major sinuses. Each sinus remains in constant communication with the nasal cavity through narrow openings or *ostia*. The sinuses are named for the bone in which they are located—frontal, ethmoid, maxillary, and sphenoidal (Fig. 36.1A). The *frontal sinuses* open into the middle meatus of the nasal cavity. The *ethmoid sinuses* consist of 3 to 15 air cells on each side of the ethmoid, with each maintaining a separate path to the nasal chamber. The anterior ethmoid, frontal, and maxillary sinuses all drain into the nasal cavity through a narrow passage called the *ostiomeatal complex* (see Fig. 36.1B). Because

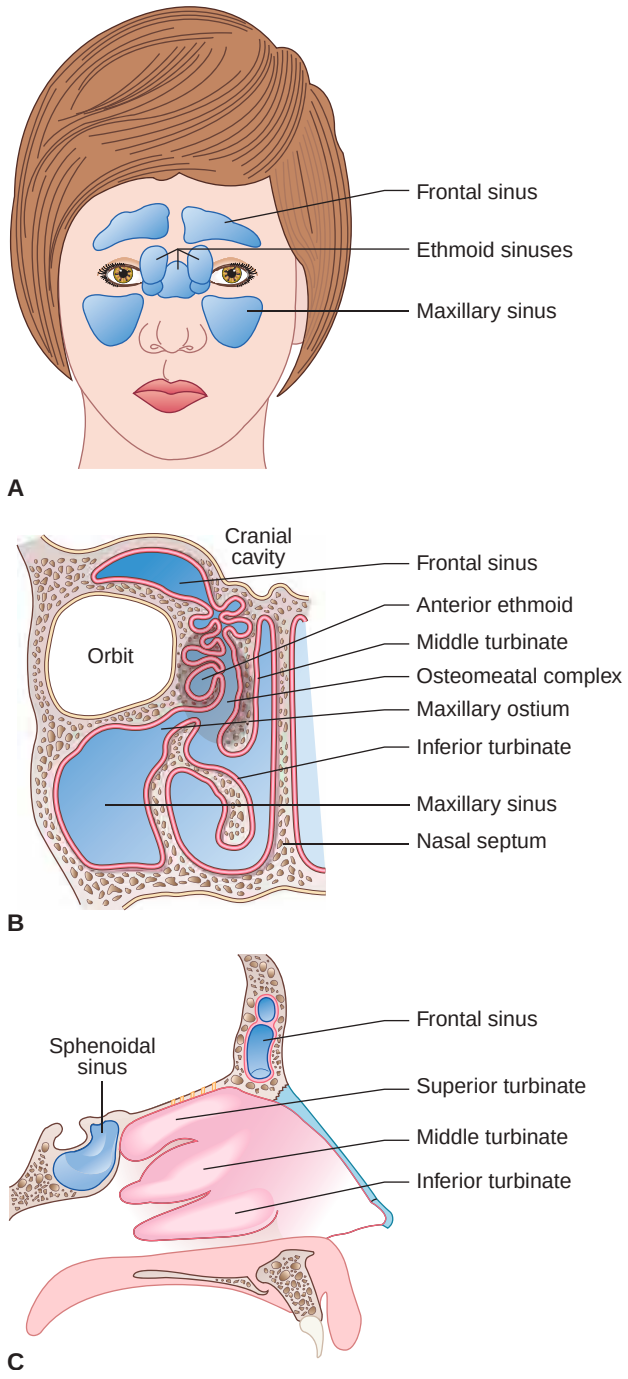


FIGURE 36.1 • Paranasal sinuses. (**A**) Frontal view showing the frontal, ethmoid, and maxillary sinuses. (**B**) Cross section of nasal cavity (anterior view). The shaded area is the osteomeatal complex, which is the final common pathway for drainage of the anterior ethmoid, frontal, and maxillary sinuses. (**C**) Lateral wall, left nasal cavity showing the frontal sphenoidal sinuses and the superior, middle, and inferior turbinates.

of this anatomic configuration, any defects in the anterior ethmoid sinus can obstruct the ostiomeatal complex and cause secondary disease of the frontal or maxillary sinuses.[9,10] The *maxillary sinuses* are located inferior to the bony orbit and superior to the hard palate, and their openings are located superiorly and medially in the sinus, a location that impedes

drainage. The *sphenoidal sinuses* are located just anterior to the pituitary fossa behind the posterior ethmoid sinuses, with their openings draining into the sphenoethmoid recess at the top of the nasal cavity (see Fig. 36.1C).

Each sinus is lined with a mucosal surface that is continuous with that of the nasal passages. An active mucociliary clearance mechanism helps move fluid and microorganisms out of the sinuses and into the nasal cavity. Mucociliary clearance, along with innate and adaptive immune mechanisms, helps to keep the sinuses sterile. The lower oxygen content in the sinuses facilitates the growth of organisms, impairs local defenses, and alters the function of immune cells.

Etiology and Pathogenesis

The most common causes of rhinosinusitis are conditions that obstruct the narrow ostia that drain the sinuses.[7] There are greater than 110 different antigenic serotypes, so it is quite possible to keep reinfecting oneself after a common cold virus.[6] Most commonly, rhinosinusitis develops when a viral upper respiratory tract infection or allergic rhinitis, which causes mucosal swelling, obstructs the ostia and impairs the mucociliary clearance mechanism. Nasal polyps also can obstruct the sinus openings and facilitate sinus infection. Infections associated with nasal polyps can be self-perpetuating because constant irritation from the infection can facilitate polyp growth. Barotrauma caused by changes in barometric pressure, as occurs in airline pilots and flight attendants, may lead to impaired sinus ventilation and clearance of secretions. Swimming, diving, and abuse of nasal decongestants are other causes of sinus irritation and impaired drainage.

Rhinosinusitis can be classified as acute, subacute, or chronic.[9] Acute rhinosinusitis may be of viral, bacterial, or mixed viral–bacterial origin and may last from 5 to 7 days in the case of acute viral rhinosinusitis and up to 4 weeks in the case of acute bacterial rhinosinusitis.[9] Recurrent acute rhinosinusitis is defined as four or more episodes of acute disease within a 12-month period. Subacute rhinosinusitis lasts from 4 weeks to less than 12 weeks, whereas chronic rhinosinusitis lasts beyond 12 weeks. Acute bacterial rhinosinusitis most commonly results from infection with *Haemophilus influenzae* or *Streptococcus pneumoniae*.[6,11]

In chronic rhinosinusitis, anaerobic organisms, including species of *Peptostreptococcus, Fusobacterium,* and *Prevotella,* tend to predominate, alone or in combination with aerobes such as the *Streptococcus* species or *Staphylococcus aureus*.[6] People with chronic rhinosinusitis and otitis media and effusion have been found to have accumulation of *Pseudomonas aeruginosa,* which forms biofilm in various ear, nose, and throat areas.[12] This finding of the presence of biofilms with chronic ear, nose, and throat infections lends support to signs and symptoms caused by the chronic inflammation related to chronic otitis, rhinosinusitis, and effusion.[12] In people who are immunocompromised (e.g., people with human immunodeficiency virus [HIV] infection), the sinuses may become infected with gram-negative species and opportunistic fungi. In this group, particularly those with prolonged neutropenia as a result of chemotherapy, the disease may have a fulminant and even fatal course.[9]

Clinical Manifestations

The symptoms of acute viral rhinosinusitis often are difficult to differentiate from those of the common cold and allergic rhinitis. They include facial pain, headache, purulent nasal discharge, decreased sense of smell, and fever. A history of a preceding common cold and the presence of purulent nasal drainage, pain on bending, unilateral maxillary pain, and pain in the teeth are common with involvement of the maxillary sinuses. The symptoms of acute viral rhinosinusitis usually resolve within 5 to 7 days without medical treatment.[6] Acute bacterial rhinosinusitis is suggested by symptoms that worsen after 5 to 7 days or persist beyond 10 days, or symptoms that are out of proportion to those usually associated with a viral upper respiratory tract infection.[9] People who are immunocompromised, such as those with leukemia, aplastic anemia, a bone marrow transplant, or HIV infection, often present with fever of unknown origin, rhinorrhea, or facial edema. Often, other signs of inflammation such as purulent drainage are absent.

In people with chronic rhinosinusitis, the only symptoms may be those such as nasal obstruction, a sense of fullness in the ears, postnasal drip, hoarseness, chronic cough, loss of taste and smell, or unpleasant breath.[12] These symptoms are often felt to be more the result of the mediators, such as histamine, bradykinin, prostaglandin, or interleukin, than the virus itself. Sinus pain is often absent. Instead, the person may complain of a headache that is dull and constant. People with chronic rhinosinusitis may have superimposed bouts of acute rhinosinusitis. The epithelial changes that occur during acute and subacute forms of rhinosinusitis usually are reversible, but the mucosal changes that occur with chronic rhinosinusitis often are irreversible.

Diagnosis and Treatment

The diagnosis of rhinosinusitis usually is based on symptom history and a physical examination that includes inspection of the nose and throat.[9–11] Headache due to sinusitis needs to be differentiated from other types of headache. Bending forward, coughing, or sneezing usually exaggerates sinusitis headache. Physical examination findings in acute bacterial sinusitis include turbinate edema, nasal crusts, and purulence of the nasal cavity.[11] Sinus radiographs and computed tomography (CT) scans may be used. CT scans usually are reserved for diagnosis of chronic rhinosinusitis or to exclude complications. Magnetic resonance imaging (MRI) is usually reserved for cases of suspected neoplasms, long-standing chronic sinusitis, or fungal sinusitis.[9]

Treatment of rhinosinusitis depends on the cause and includes appropriate use of antibiotics, mucolytic agents, and symptom relief measures. About two thirds of people with acute bacterial rhinosinusitis improve without antibiotic treatment. Most people with viral upper respiratory infections improve within 7 days. Therefore, treatment with antibiotics is usually reserved for persons who have had symptoms for more than 7 days and who present with two or more manifestations of acute bacterial rhinosinusitis (*i.e.,* purulent nasal drainage;

maxillary, tooth, or facial pain [especially if it is unilateral]; unilateral maxillary tenderness; or worsening of symptoms after initial improvement), or for those with severe symptoms.[7] In addition to antibiotic therapy, the treatment of acute rhinosinusitis includes measures to promote adequate drainage by reducing nasal congestion. Oral and topical decongestants may be used for this purpose. The use of intranasal decongestants should be limited to 3 to 5 days to prevent rebound vasodilation. Antihistamines tend to dry up secretions and are not recommended as adjunctive treatment in acute viral or bacterial rhinosinusitis. Mucolytic agents such as guaifenesin may be used to thin secretions. Topical corticosteroids may be used to decrease inflammation in persons with allergic rhinitis or rhinosinusitis. Nonpharmacologic measures include saline nasal sprays, nasal irrigation, and mist humidification. However, although no studies have been conducted, most providers feel these nasal sprays and irrigations are not effective.

Surgical intervention directed at correcting obstruction of the ostiomeatal openings may be indicated in people with chronic rhinosinusitis that is resistant to other forms of therapy. Indications for surgical intervention include obstructive nasal polyps and obstructive nasal deformities.

Complications

Because of the sinuses' proximity to the brain and orbital wall, sinusitis can lead to intracranial and orbital wall complications. Intracranial complications are seen most commonly with infection of the frontal and ethmoid sinuses because of their proximity to the dura and drainage of the veins from the frontal sinus into the dural sinus. Orbital complications can range from edema of the eyelids to orbital cellulitis and subperiosteal abscess formation. Facial swelling over the involved sinus, abnormal extraocular movements, protrusion of the eyeball, periorbital edema, or changes in mental status may indicate intracranial complications and require immediate medical attention.[6]

Influenza

Influenza is one of the most important causes of acute upper respiratory tract infection in humans. In the United States about 10% to 20% of people are diagnosed with influenza every year, and approximately 20,000 die.[13] Rates of infection are highest among children and older adults, but rates of serious illness and death are highest among people 65 years of age or older.[13]

The viruses that cause influenza belong to the Orthomyxoviridae family, whose members are characterized by a segmented, single-stranded ribonucleic acid (RNA) genome.[13] There are three types of influenza viruses that cause epidemics in humans: types A, B, and C. Influenza A differs in its ability to infect multiple species, including avian and mammalian species. The influenza A virus is further divided into subtypes based on two surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA).[13] HA is an attachment protein that allows the virus to enter epithelial cells in the respiratory tract, and NA facilitates viral replication from the cell.[13] Contagion results from the ability of the influenza A virus to develop new HA and NA subtypes against which the population is not protected. An antigenic shift, which involves a major genetic rearrangement in either antigen, may lead to epidemic or pandemic infection. Lesser changes, called *antigenic drift,* find the population partially protected by cross-reacting antibodies. Influenza B and C undergo less frequent antigenic shifts than influenza A, probably because few related viruses exist in mammalian or avian species.[13]

As with many viral respiratory tract infections, influenza is more contagious than bacterial respiratory tract infections. In contrast to the rhinoviruses, transmission occurs by inhalation of droplet nuclei rather than touching contaminated objects. Most infected people develop symptoms of the disease, increasing the likelihood of contagion through spread of infectious droplets. Young children are most likely to become infected and also to spread the infection. The incubation period for influenza is 1 to 5 days, with 2 days being the average. People become infectious starting 1 day before their symptoms begin and remain infectious through approximately 5 days after illness onset.[13] Virus shedding can continue for approximately 3 weeks.

Pathogenesis

The influenza viruses can cause three types of infections: an uncomplicated upper respiratory infection (rhinotracheitis), viral pneumonia, and a respiratory viral infection followed by a bacterial infection. Influenza initially establishes upper airway infection. In doing this, the virus first targets and kills mucous-secreting, ciliated, and other epithelial cells, leaving gaping holes between the underlying basal cells and allowing extracellular fluid to escape. This is the reason for the "runny nose" that is characteristic of this phase of the infection. If the virus spreads to the lower respiratory tract, the infection can cause severe shedding of bronchial and alveolar cells down to a single-cell–thick basal layer. Additionally, compromising the natural defenses of the respiratory tract, influenza infection promotes bacterial adhesion to epithelial cells. Pneumonia may result from a viral pathogenesis or from a secondary bacterial infection.

Clinical Manifestations

In the early stages, the symptoms of influenza often are indistinguishable from other viral infections. There is an abrupt onset of fever and chills, malaise, muscle aching, headache, profuse, watery nasal discharge, nonproductive cough, and sore throat.[13] One distinguishing feature of an influenza viral infection is the rapid onset, sometimes in as little as 1 to 2 minutes, of profound malaise. The symptoms of uncomplicated rhinotracheitis usually peak by days 3 to 5 and disappear by days 7 to 10. The aforementioned symptoms can be caused by any of the influenza A or B viruses. Influenza C virus infection causes symptoms similar to the common cold.

Viral pneumonia occurs as a complication of influenza, most frequently in older adults or in people with cardiopulmonary disease. However, it has been reported in pregnant women and in healthy, immunocompetent people. It typically develops within 1 day after onset of influenza and is characterized by rapid

progression of fever, tachypnea, tachycardia, and hypotension.[13] The clinical course of influenza pneumonia progresses rapidly. It can cause hypoxemia and death within a few days of onset. Survivors often develop diffuse pulmonary fibrosis.

Secondary complications typically include sinusitis, otitis media, bronchitis, and bacterial pneumonia.[13] People in whom secondary bacterial pneumonia develops usually report that they were beginning to feel better when they experienced a return of fever, shaking chills, pleuritic chest pain, and productive cough. The most common causes of secondary bacterial pneumonia are *S. pneumoniae*, *S. aureus*, *H. influenzae*, and *Moraxella catarrhalis*. This form of pneumonia commonly produces less tachypnea and is usually milder than primary influenza pneumonia. Influenza-related deaths can result from pneumonia as well as exacerbations of cardiopulmonary conditions and other disease. Reye syndrome (fatty liver with encephalitis) is a rare complication of influenza, particularly in young children who have been given aspirin as an antipyretic agent.

Diagnosis and Treatment

The appropriate treatment of people with influenza depends on accurate and timely diagnosis. Early diagnosis can reduce the inappropriate use of antibiotics and provide the opportunity for use of an antiviral drug. Rapid diagnostic tests, which are available for use in outpatient settings, allow health care providers to diagnose influenza more accurately, consider treatment options more carefully, and monitor the influenza type and its prevalence in their community.[13]

The goals of treatment for influenza are designed to limit the infection to the upper respiratory tract. The symptomatic approach for treatment of uncomplicated influenza rhinotracheitis focuses on rest, keeping warm, managing the fever, and keeping well hydrated. Analgesics and cough medications can also be used. Rest decreases the oxygen requirements of the body and reduces the respiratory rate and the chance of spreading the virus from the upper to lower respiratory tract. Keeping warm helps maintain the respiratory epithelium at a core body temperature of 37°C (or higher if fever is present), thereby inhibiting viral replication, which is optimal at 35°C. Drinking large amounts of liquids ensures that the function of the epithelial lining of the respiratory tract is not further compromised by dehydration. Antiviral medications may be indicated in some people. Antibacterial antibiotics should be reserved for bacterial complications.

Four antiviral drugs are available for treatment of influenza: Symmetrel (amantadine), Flumadine (rimantadine), Relenza (zanamivir), and Tamiflu (oseltamivir).[14,15] The first-generation antiviral drugs amantadine and rimantadine are similarly effective against influenza A but not influenza B. These agents inhibit the uncoating of viral RNA in the host cells and prevent its replication. Both drugs are effective in prevention of influenza A in high-risk groups and in treatment of people who acquire the disease. Unfortunately, resistance to the drugs develops rapidly, and strains that are resistant to amantadine also are resistant to rimantadine. Amantadine stimulates release of catecholamines, which can produce central nervous system side effects such as anxiety, depression, and insomnia.

The second-generation antiviral drugs zanamivir and oseltamivir are inhibitors of NA, a viral glycoprotein that is necessary for viral replication and release. These drugs, which have been approved for treatment of acute uncomplicated influenza infection, are effective against both influenza A and B viruses. Zanamivir and oseltamivir result in less resistance than amantadine and rimantadine. Zanamivir is administered intranasally, and oseltamivir is administered orally. Zanamivir can cause bronchospasm and is not recommended for people with asthma or chronic obstructive lung disease. To be effective, the antiviral drugs should be initiated within 48 hours after onset of symptoms.[13]

Influenza Immunization

Because influenza is so highly contagious, prevention relies primarily on vaccination. The formulation of the vaccines must be changed yearly in response to antigenic changes in the influenza virus. The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) annually updates its recommendations for the composition of the vaccine. Influenza vaccines are contraindicated in people with anaphylactic hypersensitivity to eggs or to other components of the vaccine, people with a history Guillain-Barré syndrome, and people with acute febrile illness.[16]

The effectiveness of the influenza vaccine in preventing and lessening the effects of influenza infection depends primarily on the age and immunocompetence of the recipient and the match between the virus strains included in the vaccine and those that circulate during the influenza season.[16] When there is a good match, the vaccine is effective in preventing the illness in approximately 70% to 90% of healthy people younger than 65 years of age.[16] Fluzone High-Dose is a new influenza vaccine for seniors older than 65 years.[16]

All people 6 months of age and older in the United States are recommended to receive the annual influenza vaccine.[16] In addition, the ACIP recommends an annual vaccine specifically for the following new high-risk populations vulnerable for serious influenza-related complications: people with BMI rates greater than 40, Alaskan Natives, and American Indians.[16]

Avian Influenza (Bird Flu)

Avian influenza, or "bird flu," is an infection caused by avian influenza viruses. The normal hosts for avian influenza viruses are birds and occasionally pigs. These influenza viruses occur naturally among birds.[17] Wild birds carry the viruses in their intestines, but usually are not affected by them. However, the virus is highly contagious among avian species and can infect and kill domestic poultry, such as chickens, ducks, and turkeys. Infected birds shed the virus in their saliva, nasal secretions, and feces. Susceptible birds become infected when they have contact with contaminated secretions or feces. Avian strains of the influenza virus do not usually cause outbreaks of disease in humans unless a reassortment of the virus genome has occurred within an intermediate mammalian host such as a pig.[17] In this setting, a virus is produced that contains mammalian characteristics as well as avian characteristics to which humans may not

be immune. It is noteworthy that many of the pandemics of the past were thought to arise in Asia, where large human populations live in close proximity to ducks, chickens, and pigs, thus facilitating the phenomenon of viral reassortment.[17]

Recently, a highly pathogenic influenza A subtype, H5N1, was found in poultry in East and Southeast Asian countries.[17] Although the H5N1 strain is highly contagious from one bird to another, its transmission from human to human is relatively inefficient and not sustained. The result is only rare cases of person-to-person transmission. Most cases occur after exposure to infected poultry or surfaces contaminated with poultry droppings. Because infection in humans is associated with a high mortality rate, there is considerable concern that the H5N1 strain might mutate and initiate a pandemic. People who contract avian flu generally complain about typical influenza symptoms along with eye infections, pneumonia, and acute RDS.[17]

There currently is no commercially available vaccine to protect humans against the bird flu. Current commercial rapid diagnostic tests are not optimally sensitive or specific for detection of the virus. Most Asian H5N1 influenza strains are resistant to amantadine and rimantadine. The NA inhibitors, oseltamivir (Tamiflu) and zanamivir (Relenza), would probably be effective if administered within 48 hours, but additional studies are needed to demonstrate their effectiveness.

Swine Flu (H1N1)

In June 2009, the World Health Organization identified a world influenza pandemic. This pandemic was caused by an influenza A flu known as the swine-origin influenza A flu (H1N1). H1N1 caused extremely high fevers and was especially serious in young adults less than 25 years of age. Interestingly, older adults were not at higher risk for H1N1 as they tend to be for most infections such as seasonal influenza. This virus is spread from human to human and is generally referred to as the swine flu. The majority of people affected by the virus did not experience severe illness although there were some who needed hospitalization and who even died. The CDC does recommend that most people be vaccinated against H1N1.

OBSTRUCTIVE AIRWAY DISORDERS

After completing this section of the chapter, you should be able to meet the following objectives:

- Describe the interaction between one's genetics, alteration of immune response, and environmental agents in the pathogenesis of asthma or reactive airway disease.
- Differentiate between chronic bronchitis and emphysema in terms of pathology and clinical manifestations.
- Describe the genetic abnormality responsible for the manifestations of cystic fibrosis.

Obstructive airway disorders are caused by disorders that limit expiratory airflow. Asthma represents an acute and reversible form of airway disease caused by narrowing of airways due to bronchospasm, inflammation, and increased airway secretions. Chronic obstructive disorders include a variety of airway diseases, such as chronic bronchitis, emphysema, bronchiectasis, and CF.

Physiology of Airway Disease

Air moves through the upper airways (*i.e.,* trachea and major bronchi) into the lower or pulmonary airways (*i.e.,* bronchi and alveoli). In the pulmonary airways, the cartilaginous layer that provides support for the trachea and major bronchi gradually disappears and is replaced with crisscrossing strips of smooth muscle. The contraction and relaxation of the smooth muscle layer, which is innervated by the autonomic nervous system, controls the diameter of the bronchial airways and consequent resistance to airflow. Parasympathetic stimulation, through the vagus nerve and cholinergic receptors, produces bronchial constriction, whereas sympathetic stimulation, through β_2-adrenergic receptors, increases bronchial dilation. At rest, a slight vagal-mediated bronchoconstrictor tone predominates. When there is need for increased airflow, as during exercise, the bronchodilator effects of the sympathetic nervous system are stimulated and the bronchoconstrictor effects of the parasympathetic nervous system are inhibited. Bronchial smooth muscle also responds to inflammatory mediators, such as histamine, that act directly on bronchial smooth muscle cells to produce constriction.

KEY POINTS

AIRWAY DISORDERS

- Changes in airway patency involve changes in airway diameter due to bronchial smooth muscle hyperreactivity or changes in bronchial wall structure, injury to the mucosal lining of the airways, or excess respiratory tract secretions.
- Bronchial asthma is a chronic disorder of the airways that causes episodes of airway obstruction due to bronchial smooth muscle hyperreactivity and airway inflammation. The episodes usually are reversible.
- COPD represents a group of disorders that cause chronic and recurrent obstruction of the pulmonary airways. These disorders can affect patency of the bronchial structures (chronic bronchitis), the gas-diffusing airspaces distal to the terminal bronchioles (emphysema), or a combination of both.

Asthma

Asthma is a chronic disorder of the airways that causes episodes of airway obstruction, bronchial hyperresponsiveness, airway inflammation, and, in some, airway remodeling.[12] According to 2009 data, an estimated 7.1 million American children, which is 9.6% of all American children, have asthma.[12] An estimated 17.5 million American adults have asthma, which is approximately 7.7% of all adults.[12] Even though many diseases have decreased mortality rates in the United States, the mortality rate for asthma has increased, especially with older adults (>85 years) and African Americans.[13]

The strongest risk factor for developing asthma is a genetic predisposition for the development of an immunoglobulin E (IgE)-mediated response to common allergens.[14] IgE is the antibody involved in causing allergic reactions and inflammation.[14] Other risk factors for childhood asthma include family history of asthma, allergies, antenatal exposure to tobacco smoke and pollution, and multiple potentially overlapping genetic predispositions.[15] Asthma severity is impacted by several factors including genetics, age of onset, pollution exposure, atopy, degree of exposure to triggers, environmental triggers such as tobacco smoke and dust mites, and the presence of gastroesophageal reflux disease or respiratory infections[13] (see "Severe or Refractory Asthma"). Reflux during sleep can also contribute to nocturnal asthma.[14]

Etiology and Pathogenesis

The common denominator underlying asthma is an exaggerated hyperresponsiveness to a variety of stimuli. Airway inflammation manifested by the presence of inflammatory cells (particularly eosinophils, lymphocytes, and mast cells) and by damage to the bronchial epithelium contributes to the pathogenesis of the disease. There are two subsets of T-helper cells (T_1H and T_2H) that develop from the same precursor $CD4^+$ T lymphocyte.[16–18] T_1H cells differentiate in response to microbes and stimulate the differentiation of B cells into immunoglobulin (Ig)M– and IgG-producing plasma cells. T_2H cells, on the other hand, respond to allergens and helminths (intestinal parasites) by stimulating B cells to differentiate into IgE-producing plasma cells, produce growth factors for mast cells, and recruit and activate eosinophils. In people with allergic asthma, T-cell differentiation appears to be skewed toward a proinflammatory T_2H response. Although the molecular basis for this preferential differentiation is unclear, it seems likely that both genetic and environmental factors play a role.[16–19]

Cytokines also have an apparent role in the chronic inflammatory response and complications of asthma. Tumor necrosis factor (TNF)-α and interleukins 4 and 5 (IL-4, IL-5) participate in the pathogenesis of bronchial asthma through their effects on the bronchial epithelial and smooth muscle cells.[20–22] Studies suggest that TNF-α, an inflammatory cytokine that is stored and released from mast cells, plays a critical role in the initiation and amplification of airway inflammation in persons with asthma. TNF-α is credited with increasing the migration and activation of inflammatory cells (*i.e.,* eosinophils and neutrophils) and contributing to all aspects of airway remodeling, including proliferation and activation of fibroblasts, increased production of extracellular matrix glycoproteins, and mucous cell hyperplasia.[22]

It has been determined that frequent viral respiratory infections predispose people with asthma to experience an exacerbation of their disease. In fact, frequent viral respiratory infections may also cause the development of asthma in some people.[17] When these respiratory infections are frequent at an early age, there is evidence that the T-helper 2 (T_2H) response is exaggerated. When the CD4 T_2H cytokines IL-4, IL-5, and IL-13 are released, the airways are predisposed for an allergic response, which favors the production of IgE.[16–18]

The National Heart, Lung, and Blood Institute's Expert Panel Report 3 (NHLBI EPR 3): Guidelines for the Diagnosis and Management of Asthma defined asthma as a chronic inflammatory disorder of the airways. The immunological aspects of asthma including the cascade of neutrophils, eosinophils, lymphocytes, and mast cells cause epithelial injury. This causes airway inflammation, which further increases hyperresponsiveness and decreased airflow.[14] There are multiple mediators and cell types that cause the inflammation and airway bronchoconstriction in asthma. When mast cells are activated, the release of histamine; prostaglandin D_2; cytokines such as IL-1 to IL-5, interferon, TNF, and granulocyte–macrophage colony-stimulating factor; and leukotrienes causes massive bronchoconstriction and inflammation of pulmonary vasculature endothelium. Mast cells can trigger multiple cytokine release, which causes major inflammation of the airway. The contraction of the airways and subsequent swelling leads to further airway obstruction.

The mast cell release may be linked to exercise-induced asthma (EIA), which is when individuals only experience wheezing and bronchospasm during exercise.[19,20] The cause of EIA is unclear but the following two theories are possible explanations. One theory explaining the cause of EIA is based

on the loss of heat and water from the tracheobronchial tree because of the need for warming and humidifying large volumes of air.[21] The response commonly is exaggerated when the person exercises in a cold environment. The second theory supporting EIA is the airway rewarming hypothesis, which states that airways cool and then warm during any exercise.[21] This causes congestion in the bronchiolar vessels that surround the bronchial tree and allows fluid exudates to move into the mucosa of the airway, which triggers the inflammatory cascade. It is important to assess the type of air (polluted, cold, or warm), level of exercise, presence/absence of respiratory infectious process, and individual's asthma stability when identifying if a person has EIA.[19]

Eosinophils tend to be present in airways of people with asthma and generate inflammatory enzymes and release leukotrienes and many proinflammatory enzymes.[14,22] It is common to have increased neutrophils in sputum and airways of people experiencing asthma exacerbations.[22] The release of leukotrienes causes more mucus secretion, which often obstructs the airway further and causes more histamine release from the mast cells.[21]

This inflammatory process produces recurrent episodes of airway obstruction, characterized by wheezing, breathlessness, chest tightness, and a cough that often is worse at night and in the early morning. These episodes, which usually are reversible either spontaneously or with treatment, also cause an associated increase in bronchial responsiveness to a variety of stimuli.[17] Chronic inflammation can lead to airway remodeling, in which case airflow limitations may be only partially reversible.[14] This may be due to the long-term effects of the inflammation on the airway structures.[14]

There is a small group of people with the clinical triad of asthma, chronic rhinosinusitis with nasal polyps, and precipitation of asthma and rhinitis attacks in response to aspirin and other NSAIDs.[22] The mechanism of the hypersensitivity reaction is complex and not fully understood, but most evidence points toward an abnormality in arachidonic acid (AA) metabolism. Cyclooxygenase (COX), the rate-limiting enzyme in AA metabolism, exists in two main forms: COX-1 and COX-2. COX-1 is responsible for the synthesis of protective prostaglandins and COX-2 for the synthesis of mediators of inflammation and bronchoconstriction. It has been hypothesized that in people with aspirin-induced asthma, the inhibition of COX-1 shunts the metabolism of AA away from the production of protective prostaglandins and toward the generation of COX-2 and other mediators of inflammation and bronchoconstriction.[22] Avoidance of aspirin and all NSAIDs is a necessary part of the treatment program.

In addition, both emotional factors and changes in hormone levels are thought to contribute to an increase in asthma symptoms. Emotional factors produce bronchospasm by way of vagal pathways. They can act as a bronchospastic trigger, or they can increase airway responsiveness to other triggers through noninflammatory mechanisms. The role of sex hormones in asthma is unclear, although there is much circumstantial evidence to suggest that they may be important. In fact, research shows girls with an early menarche (<11.5 years) had twice the chance of developing asthma in their twenties than girls with average menarche.[23] Up to 40% of women with asthma report a premenstrual increase in asthma symptoms.[24] Female sex hormones have a regulatory role on β_2-adrenergic function, and it has been suggested that abnormal regulation may be a possible mechanism for premenstrual asthma.[24] A study comparing premenopausal women with asthma, menopausal women with asthma, and a control group found that menopausal women with asthma had decreased estradiol concentrations, had high sputum neutrophils, and exhaled IL-6, which is indicative of a neutrophilic inflammation. Women with premenopausal asthma had an eosinophilic inflammatory phenotype.[24]

Clinical Manifestations

Asthma attacks may occur spontaneously or in response to various triggers, respiratory infections, emotional stress, or weather changes. Asthma is often worse at night, referred to as *nocturnal asthma*. Studies of nocturnal asthma suggest that there is a circadian and sleep-related variation in hormones and respiratory function.[25,26] The greatest decrease in respiratory function occurs at about 4:00 AM, at which time cortisol levels are low, melatonin levels high, and eosinophil activity increased.

People with asthma exhibit a wide range of signs and symptoms, from episodic wheezing and feelings of chest tightness to an acute, immobilizing attack. The attacks differ from person to person, and between attacks, many people are symptom-free. A mild attack may produce a feeling of chest tightness, a slight increase in respiratory rate with prolonged expiration, and mild wheezing. A cough may accompany the wheezing. More severe attacks are accompanied by use of the accessory muscles, distant breath sounds due to air trapping, and loud wheezing. As the condition progresses, fatigue develops, the skin becomes moist, and anxiety and apprehension are obvious. Sensations of shortness of breath may be severe, and often the person is able to speak only one or two words before taking a breath. At the point at which airflow is markedly decreased, breath sounds become inaudible with diminished wheezing, and the cough becomes ineffective despite being repetitive and hacking.[17] This point often marks the onset of respiratory failure.

During an asthmatic attack, the airways narrow because of bronchospasm, edema of the bronchial mucosa, and mucus plugging. Expiration becomes prolonged because of progressive airway obstruction. The amount of air that can be forcibly expired in 1 second (forced expiratory volume in 1 second [$FEV_{1.0}$]) and the peak expiratory flow (PEF) rate, measured in liters per second, are decreased. A fall in the PEF to levels below 50% of the predicted value during an acute asthmatic attack indicates a severe exacerbation and the need for emergency department treatment.[17]

During a prolonged attack, air becomes trapped behind the occluded and narrowed airways, causing hyperinflation of the lungs. This produces an increase in the residual volume (RV) along with a decrease in the inspiratory reserve capacity (tidal volume + inspiratory reserve volume [IRC]) and forced vital capacity (FVC), such that the person breathes close to his or

her functional residual capacity (residual volume + expiratory reserve volume). As a result, more energy is needed to overcome the tension already present in the lungs, and the accessory muscles (*e.g.,* sternocleidomastoid muscles) are required to maintain ventilation and gas exchange. This increased work of breathing further increases oxygen demands and causes dyspnea and fatigue. Because air is trapped in the alveoli and inspiration is occurring at higher residual lung volumes, the cough becomes less effective. As the condition progresses, the effectiveness of alveolar ventilation declines, and mismatching of ventilation and perfusion occurs, causing hypoxemia and hypercapnia. Pulmonary vascular resistance may increase as a result of the hypoxemia and hyperinflation, leading to a rise in pulmonary arterial pressure and increased work demands on the right heart.

Diagnosis

The diagnosis of asthma is based on a careful history and physical examination, laboratory findings, and pulmonary function studies. Spirometry provides a means for measuring FVC, $FEV_{1.0}$, PEF, tidal volume, expiratory reserve capacity, and inspiratory reserve capacity. The $FEV_{1.0}$/FVC ratio can then be calculated. The level of airway responsiveness can be measured by inhalation challenge tests using methacholine (a cholinergic agonist), histamine, or exposure to a nonpharmacologic agent such as cold air.

Small, inexpensive, portable meters that measure PEF are available. Although not intended for use in the diagnosis of asthma, they can be used in clinics and primary care providers' offices and in the home to provide frequent measures of flow rates. Day–night (circadian) variations in asthma symptoms and PEF variability can be used to indicate the severity of bronchial hyperresponsiveness. The person's best performance is established from readings taken over several weeks. This often is referred to as the individual's *personal best* and is used as a reference to indicate changes in respiratory function.[14]

Treatment

The NHLBI EPR 3 classifies four stages of asthma for children greater than 12 years and adults, including intermittent, mild persistent, moderate persistent, and severe persistent.[17] The Expert Panel developed these classification systems in order to direct asthma treatment and to assist in identifying people at high risk for development of life-threatening asthma attacks[14,15] (Table 37.1). Asthma treatment consists of prevention measures, nonpharmacological measures, desensitization, and pharmacologic management.

Prevention measures to control factors contributing to asthma severity are aimed at limiting exposure to irritants and factors that increase asthma symptoms and precipitate asthma exacerbations. They include education of the person and family regarding measures used in avoiding exposure to irritants and allergens that are known to induce or trigger an attack. A careful history often is needed to identify all the contributory factors. Factors such as nasal polyps, a history of aspirin sensitivity, and gastroesophageal reflux should be considered. Annual influenza vaccination is recommended for people with persistent asthma.

Nonpharmacological management includes relaxation techniques and controlled breathing, which often help to allay the panic and anxiety that aggravate breathing difficulties. The hyperventilation that often accompanies anxiety and panic is known to act as an asthmatic trigger. In a child, measures to encourage independence as it relates to symptom control, along with those directed at helping to develop a positive self-concept, are essential.

TABLE 37.1 CLASSIFICATION OF ASTHMA SEVERITY

	SYMPTOMS	NIGHTTIME SYMPTOMS	LUNG FUNCTION
Mild intermittent	Symptoms ≤2 times a week Asymptomatic and normal PEF between exacerbations Exacerbations brief (from a few hours to a few days); intensity may vary.	≤2 times a month	$FEV_{1.0}$ or PEF ≥80% predicted PEF variability <20%
Mild persistent	Symptoms >2 times a week but <1 time a day Exacerbations may affect activity.	>2 times a month	$FEV_{1.0}$ or PEF ≥80% predicted PEF variability 20%–30%
Moderate persistent	Daily symptoms Daily use of inhaled short-acting β_2-adrenergic agonist Exacerbations affect activity. Exacerbations ≥2 times a week; may last days	>1 time a week	$FEV_{1.0}$ or PEF >60%–<80% predicted PEF variability >30%
Severe persistent	Continual symptoms Limited physical activity Frequent exacerbations	Frequent	$FEV_{1.0}$ or PEF ≤60% predicted PEF variability >30%

$FEV_{1.0}$, forced expiratory volume in 1 second; PEF, peak expiratory flow rate.

Adapted from National Asthma Education and Prevention Program. (2003). Expert Panel report 2: Guidelines for the diagnosis and management of asthma: Update of selected topics—2002. National Institutes of Health publication no. 02-5074. Bethesda, MD: National Institutes of Health.

A *program of desensitization* may be undertaken in people with persistent asthma who react to allergens, such as house dust mites, that cannot be avoided. This involves the injection of selected antigens (based on skin tests) to stimulate the production of IgG antibodies that block the IgE response. A course of allergen immunotherapy is typically of 3 to 5 years' duration.[14]

The Expert Panel recommends a stepwise approach to *pharmacologic therapy* based on the classification systems discussed previously.[14] The first line of treatment with any of the persistent forms of asthma includes an inflammatory controller drug that would include inhaled corticosteroids (ICS), mast cell stabilizers, and leukotriene modifiers. ICS are considered the most effective in preventing airway inflammation and generally the drug used.

The *quick-relief medications* such as the short-acting β_2-adrenergic agonists (SABA) (*e.g.,* albuterol, levalbuterol, pirbuterol) relax bronchial smooth muscle and provide prompt relief of symptoms, usually within 30 minutes. They are administered by inhalation (*i.e.,* metered-dose inhaler [MDI] or nebulizer), and their recommended use is in alleviating acute attacks of asthma because regular use does not produce beneficial effects.[14] The anticholinergic medications (*e.g.,* ipratropium) block the postganglionic efferent vagal pathways that cause bronchoconstriction. These medications, which are administered by inhalation, produce bronchodilation by direct action on the large airways and do not change the composition or viscosity of the bronchial mucus. It is thought that they may provide some additive benefit for treatment of asthma exacerbations when administered with inhaled β_2-adrenergic agonists.[14] A short course of systemic corticosteroids, administered orally or parenterally, may be used for treating an acute flare. Although their onset of action is slow (>4 hours), systemic corticosteroids may be used in the treatment of moderate to severe exacerbations because of their action in preventing the progression of the exacerbation, speeding recovery, and preventing early relapses.[14]

The anti-inflammatory agents sodium cromolyn and nedocromil are also used to prevent an asthmatic attack. These agents act by stabilizing mast cells, thereby preventing release of the inflammatory mediators that cause an asthmatic attack. They are used prophylactically to prevent early and late responses but are of no benefit when taken during an attack. Due to the immunomodulatory properties of vitamin D and its abilities to modify proinflammatory and anti-inflammatory responses in the immunological system, there have been studies suggesting a correlation of vitamin D and more effective management of childhood and asthma exacerbations as well as with steroid-resistant asthma.[27]

Severe or Refractory Asthma

Severe or refractory asthma represents a subgroup of approximately 5% of people with asthma who have more troublesome disease as evidenced by high medication requirements to maintain good symptom control or those who continue to have persistent symptoms despite high medication use.[30] These people are at increased risk for fatal or near-fatal asthma.

Little is known about the causes of severe asthma. Among the proposed risk factors are genetic predisposition, continued allergen or tobacco exposure, infection, intercurrent sinusitis or gastroesophageal reflux disease, and lack of compliance or adherence with treatment measures.[30] It has been proposed that because asthma is a disease involving multiple genes, mutations in genes regulating cytokines, growth factors, or receptors for medications used in treatment of asthma (β_2-adrenergic agonist or glucocorticoid) could be involved. Environmental factors include both allergen and tobacco exposure, with the strongest response occurring in response to house dust, cockroach allergen, and *Alternaria* exposure. Infections may also play a role. Respiratory syncytial virus infections are implicated in children, and pathogens such as mycoplasma and chlamydiae may play a role in adults. Gastroesophageal reflux and chronic sinusitis may also play a role. Although the cause of death during an acute asthmatic attack is largely unknown, both cardiac arrhythmias and asphyxia due to severe airway obstruction have been implicated. It has been suggested that an underestimation of the severity of the attack may be a contributing factor. Deterioration often occurs rapidly during an acute attack, and underestimation of its severity may lead to a life-threatening delay in seeking medical attention. Frequent and repetitive use of β_2-adrenergic agonist inhalers far in excess of the recommended doses may temporarily blunt symptoms and mask the severity of the condition. It has been suggested that people who have a fatal or near-fatal asthmatic attack may not perceive its severity.[31] That is, they may not perceive the severity of their condition and consequently not take appropriate measures in terms of seeking medical or emergency treatment.

The long-acting beta$_2$-agonists (LABA) such as salmeterol and formoterol are used to treat severe refractory asthma only if no other treatment is effective. The long-acting β_2-adrenergic agonists have durations of action of at least 12 hours and should not be used to treat acute symptoms or exacerbations. These drugs have a black box warning from the U.S. Food and Drug Administration due to their possibility of causing asthma death, especially if they are used as a monotherapy. Research is also focusing on the use of allergen immunotherapy treatment aimed at T_2H cytokines in specific groups of people with severe asthma. However, only one is currently available.[28,29] The only licensed anti-IgE therapy for severe asthma is omalizumab, which has severe potential systemic side effects.[29]

Asthma in Older Adults

For older adults with asthma, who already have a decreased immunological function due to aging, it is important to be aware of how this lowered immunity impacts their airway inflammation. Studies demonstrate these changes in immune function can seriously affect their conditions.[32]

Asthma in Children

Asthma is a leading cause of chronic illness in children and is responsible for approximately 14.4 million number of lost school days/year. It is the most frequent admitting diagnosis

in children's hospitals. Based on information collected by the Centers for Disease Control and Prevention, asthma may have its onset at any age. In addition, asthma is more prevalent in black than white children and results in more frequent disability and more frequent hospitalizations in black children.[33]

As with adults, asthma in children commonly is associated with an IgE-related reaction. It has been suggested that IgE directed against respiratory viruses in particular may be important in the pathogenesis of wheezing illnesses in infants (*i.e.,* bronchiolitis), which often precede the onset of asthma. Other contributing factors include exposure to environmental allergens such as pet dander, dust mite antigens, and cockroach allergens. Exposure to environmental tobacco smoke also contributes to asthma in children.

The signs and symptoms of asthma in infants and small children vary with the stage and severity of an attack. Because airway patency decreases at night, many children have acute signs of asthma at this time. Often, previously well infants and children develop what may seem to be a cold with rhinorrhea, rapidly followed by irritability, a tight and nonproductive cough, wheezing, tachypnea, dyspnea with prolonged expiration, and use of accessory muscles of respiration. Cyanosis, hyperinflation of the chest, and tachycardia indicate increasing severity of the attack. Wheezing may be absent in children with extreme respiratory distress. The symptoms may progress rapidly and require a trip to the emergency department or hospitalization.

The Expert Panel of the NAEPP has developed guidelines for management of asthma in infants and children from 0 to 4 years, 5 to 11 years, and for adults and children older than 12 years of age.[14] As with adults and older children, the Expert Panel recommends a stepwise approach to diagnosing and managing asthma in infants and children from 0 to 4 years and from 5 to 11 years.[14,34]

Chronic Obstructive Pulmonary Disease

COPD is characterized by chronic and recurrent obstruction of airflow in the pulmonary airways. Airflow obstruction usually is progressive and is accompanied by inflammatory responses to noxious particles or gases. COPD is a leading cause of morbidity and mortality worldwide. It has been estimated that approximately 24 million Americans[43] have some degree of COPD and 12.1 million are diagnosed with COPD. COPD is the fourth leading cause of death in the United States.[35] In 2006, COPD claimed the lives of more than 120,970 people in the United States, with the number of women dying from the disease surpassing that of men.[35] According to the National Heart, Lung, and Blood Institute, the national projected annual cost for COPD in 2010 was $49.9 billion.[36]

The most common cause of COPD is smoking, as evidenced by the fact that 80% to 85% of people with COPD have a history of smoking.[45] A second, less common factor is a hereditary deficiency in α_1-antitrypsin. Other predisposing factors are asthma and airway hyperresponsiveness. Unfortunately, clinical findings are almost always absent during the early stages of COPD, and as many as 50% of smokers may have undiagnosed COPD.[37] By the time symptoms appear or are recognized, the disease is usually far advanced. For smokers with early signs of airway disease, there is hope that early recognition, combined with appropriate treatment and smoking cessation, may prevent or delay the usually relentless progression of the disease.

Etiology and Pathogenesis

The mechanisms involved in the pathogenesis of COPD usually are multiple and include inflammation and fibrosis of the bronchial wall, hypertrophy of the submucosal glands and hypersecretion of mucus, and loss of elastic lung fibers and alveolar tissue.[37] Inflammation and fibrosis of the bronchial wall, along with excess mucus secretion, obstruct airflow and cause mismatching of ventilation and perfusion. Destruction of alveolar tissue decreases the surface area for gas exchange, and loss of elastic fibers impairs the expiratory flow rate, increases air trapping, and predisposes to airway collapse.

The term *chronic obstructive pulmonary disease* encompasses two types of obstructive airway disease: *emphysema,* with enlargement of airspaces and destruction of lung tissue, and *chronic obstructive bronchitis,* with increased mucus production, obstruction of small airways, and a chronic productive cough. People with COPD often have overlapping features of both disorders.

Emphysema. Emphysema is characterized by a loss of lung elasticity and abnormal enlargement of the airspaces distal to the terminal bronchioles, with destruction of the alveolar walls and capillary beds (Fig. 37.9). Enlargement of the airspaces leads to hyperinflation of the lungs and produces an increase in total lung capacity (TLC). Two of the recognized causes of emphysema are smoking, which incites lung injury, and an inherited deficiency of α_1-antitrypsin, an antiprotease enzyme that protects the lung from injury. AAT deficiency is the second most severe genetic problem affecting the lungs and is a result of a mutated ATT gene at gene locus 14.[38] ATT is a protease inhibitor that helps to protect the lung from protease enzymes such as neutrophil elastase, which damages healthy lung tissue as well as assists in removing bacteria during acute respiratory dysfunction.[38]

Emphysema is thought to result from the breakdown of elastin and other alveolar wall components by enzymes, called *proteases,* which digest proteins. Normally, antiprotease enzymes, including α_1-antitrypsin, protect the lung. Cigarette smoke and other irritants stimulate the movement of inflammatory cells into the lungs, resulting in increased release of elastase and other proteases. In smokers in whom COPD develops, antiprotease production and release may be inadequate to neutralize the excess protease production such that the process of elastic tissue destruction goes unchecked (Fig. 37.10).

The type and amount of α_1-antitrypsin that a person has is determined by a pair of codominant genes referred to as

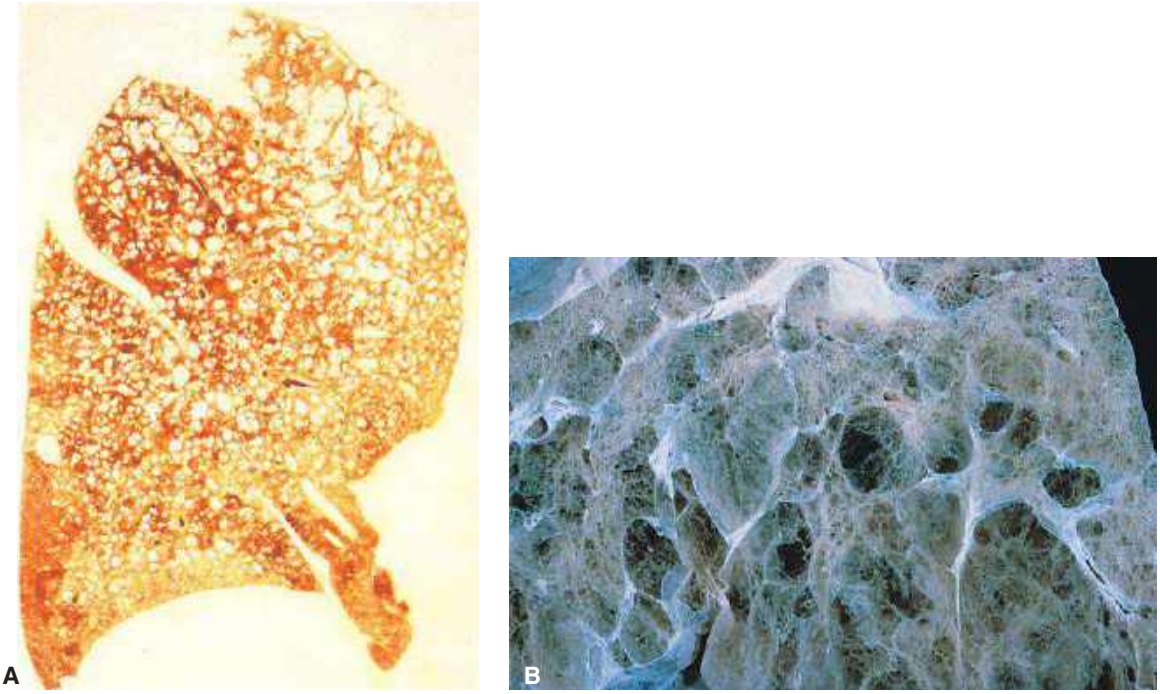


FIGURE 37.9 • Panacinar emphysema. (**A**) A whole mount of the left lung from a person with severe emphysema reveals widespread destruction of pulmonary parenchyma that in some areas leaves behind a lacy network of supporting tissue. (**B**) The lung from a person with α_1-antitrypsin deficiency shows a panacinar pattern of emphysema. The loss of alveolar walls has resulted in markedly enlarged airspaces. (From Rubin R., Strayer D. (Eds.). (2012). *Rubin's pathology: Clinicopathologic foundations of medicine* (6th ed., p. 569). Philadelphia, PA: Lippincott Williams & Wilkins.)

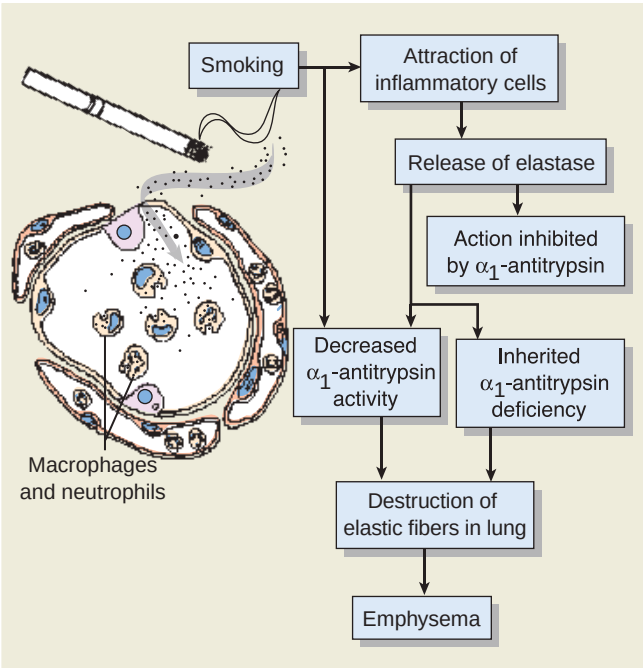


FIGURE 37.10 • Protease (elastase)–antiprotease (antitrypsin) mechanisms of emphysema. The effects of smoking and an inherited α_1-antitrypsin deficiency on the destruction of elastic fibers in the lung and development of emphysema are shown.

PI (protein inhibitor) genes. An α_1-antitrypsin deficiency is inherited as an autosomal recessive disorder. There are more than 75 mutations of the gene. ATT deficiency is most common in people of Scandinavian descent. Most people with clinically diagnosed emphysema before the age of 40 years have an α_1-antitrypsin deficiency. Smoking and repeated respiratory tract infections, which also decrease α_1-antitrypsin levels, contribute to the risk for emphysema in persons with α_1-antitrypsin deficiency. Laboratory methods are available for measuring α_1-antitrypsin levels. Human α_1-antitrypsin is available for replacement therapy in people with a hereditary deficiency of the enzyme.

There are two commonly recognized types of emphysema: centriacinar or centrilobular, and panacinar (Fig. 37.11). The centriacinar type affects the bronchioles in the central part of the respiratory lobule, with initial preservation of the alveolar ducts and sacs.[37] It is the most common type of emphysema and is seen predominantly in male smokers. The panacinar type produces initial involvement of the peripheral alveoli and later extends to involve the more central bronchioles. This type of emphysema is more common in people with α_1-antitrypsin deficiency. It also is found in smokers in association with centriacinar emphysema. In such cases, the panacinar pattern tends to occur in the lower parts of the lung and centriacinar emphysema is seen in the upper parts of the lung.

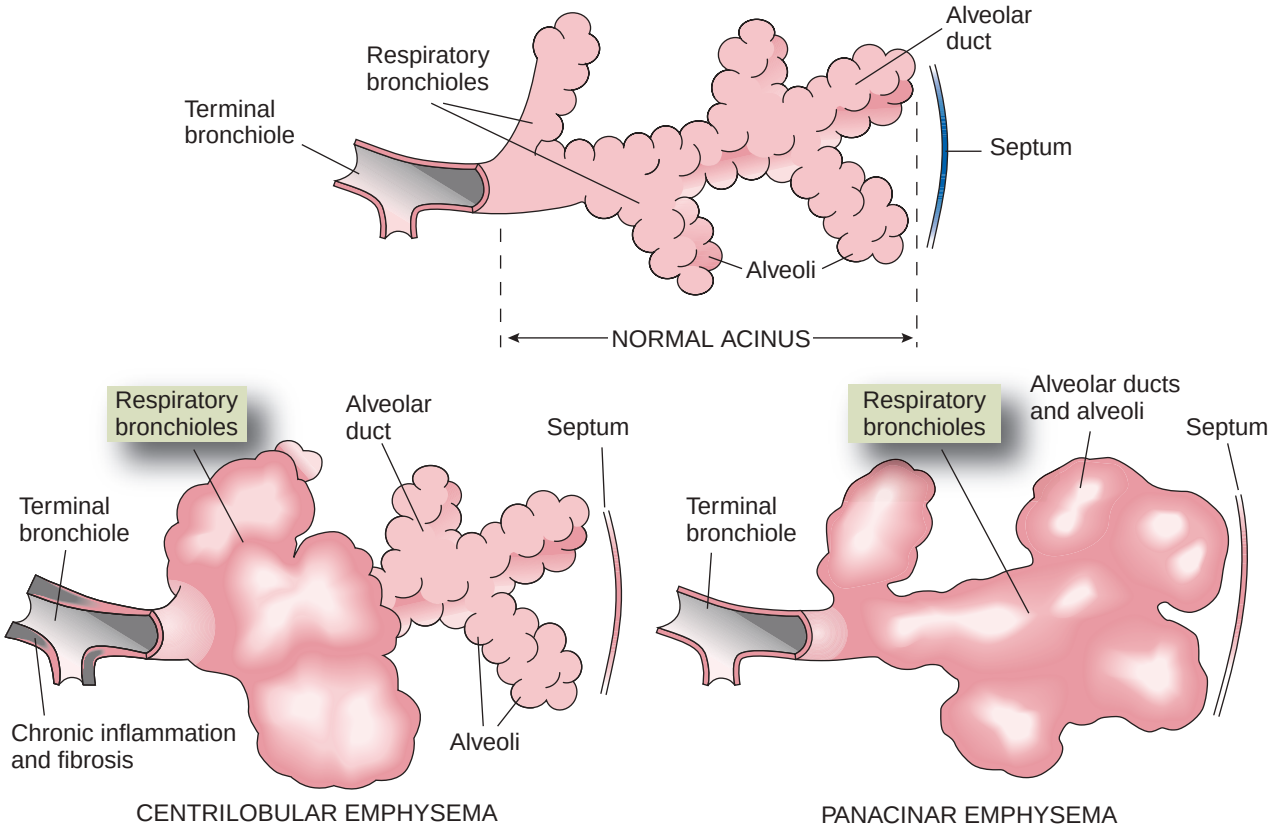


FIGURE 37.11 • Centriacinar panacinar and paraseptal are the types of emphysema. (From Rubin R., Strayer D. (Eds.). (2012). *Rubin's pathology: Clinicopathologic foundations of medicine* (6th ed.). Philadelphia, PA: Lippincott Williams & Wilkins.)

Chronic Bronchitis. Chronic bronchitis represents airway obstruction of the major and small airways.[37] The condition is seen most commonly in middle-aged men and is associated with chronic irritation from smoking and recurrent infections. A clinical diagnosis of chronic bronchitis requires the history of a chronic productive cough for at least 3 consecutive months in at least 2 consecutive years.[48] Typically, the cough has been present for many years, with a gradual increase in acute exacerbations that produce frankly purulent sputum.

The earliest feature of chronic bronchitis is hypersecretion of mucus in the large airways, associated with hypertrophy of the submucosal glands in the trachea and bronchi.[37] Although mucus hypersecretion in the large airways is the cause of sputum overproduction, it is now thought that accompanying changes in the small airways (small bronchi and bronchioles) are physiologically important in the airway obstruction that develops in chronic bronchitis.[37] Histologically, these changes include a marked increase in goblet cells and excess mucus production with plugging of the airway lumen, inflammatory infiltration, and fibrosis of the bronchiolar wall. It is thought that both the submucosal hypertrophy in the larger airways and the increase in goblet cells in the smaller airways are a protective reaction against tobacco smoke and other pollutants. Viral and bacterial infections are common in people with chronic bronchitis and are thought to be a result rather than a cause of the problem.

Clinical Manifestations

The clinical manifestations of COPD usually have an insidious onset. People characteristically seek medical attention in the fifth or sixth decade of life, with manifestations such as fatigue, exercise intolerance, cough, sputum production, or shortness of breath. The productive cough usually occurs in the morning and the dyspnea becomes more severe as the disease progresses. Frequent exacerbations of infection and respiratory insufficiency are common, causing absence from work and eventual disability. The late stages of COPD are characterized by recurrent respiratory infections and chronic respiratory failure. Death usually occurs during an exacerbation of illness associated with infection and respiratory failure.

The mnemonics "pink puffer" and "blue bloater" have been used to differentiate the clinical manifestations of emphysema and chronic obstructive bronchitis. People with predominant emphysema are classically referred to as *pink puffers,* a reference to the lack of cyanosis, the use of accessory muscles, and pursed-lip ("puffer") breathing. With loss of lung elasticity and hyperinflation of the lungs, the airways often collapse during expiration because pressure in surrounding lung tissues exceeds airway pressure. Air becomes trapped

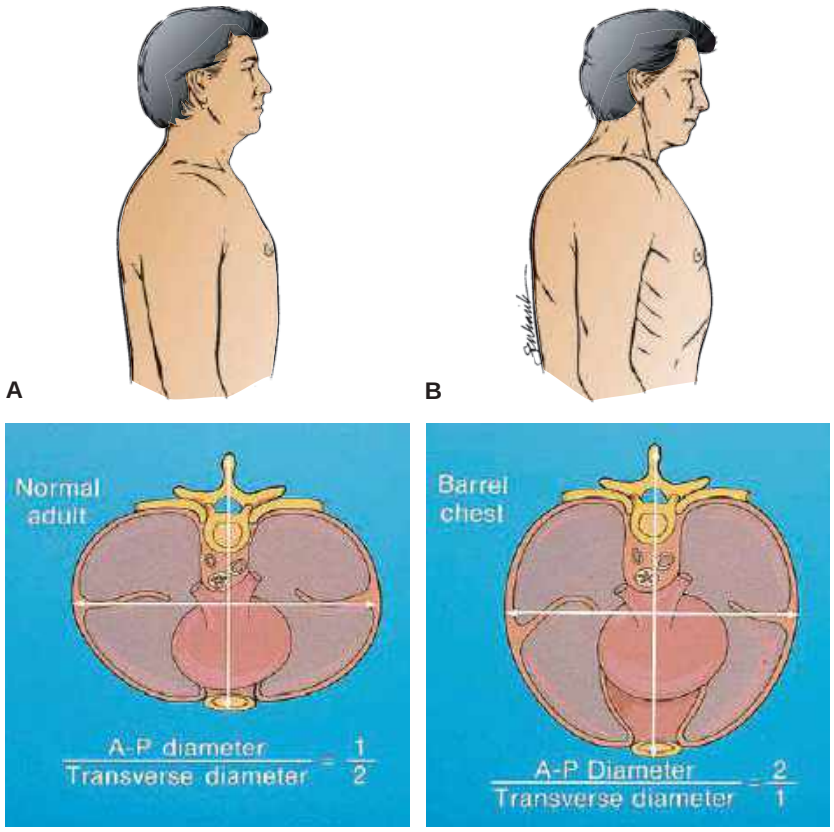


FIGURE 37.12 • Characteristics of normal chest wall and chest wall in emphysema. The normal chest wall and its cross-section are illustrated on the left (**A**). The barrel-shaped chest of emphysema and its cross-section are illustrated on the right (**B**). (From Smeltzer S. C., Bare B., Hinkle J., et al. (2010). *Brunner and Suddarth's textbook of medical-surgical nursing* (12th ed., p. 604). Philadelphia, PA: Lippincott Williams & Wilkins.)

in the alveoli and lungs, producing an increase in the anteroposterior dimensions of the chest, the so-called *barrel chest* that is typical of people with emphysema (Fig. 37.12). Such people have a dramatic decrease in breath sounds throughout the chest. Because the diaphragm may be functioning near its maximum ability, the person is vulnerable to diaphragmatic fatigue and acute respiratory failure.

People with a clinical syndrome of chronic bronchitis are classically labeled *blue bloaters,* a reference to cyanosis and fluid retention associated with right-sided heart failure. In practice, differentiation between the two types of COPD is often difficult. This is because people with COPD often have some degree of both emphysema and chronic bronchitis.

The manifestations of COPD represent a progressive change in respiratory function. There is moderate to severe respiratory impairment due to obstruction of airflow, which is greater on expiration than inspiration, resulting in increased work of breathing but decreased effectiveness. The development of exertional dyspnea, often described as increased effort to breathe, heaviness, air hunger, or gasping, can be insidious and is often reported in the sixth decade. Activities involving significant arm work, particularly above the shoulders, are particularly difficult for persons with COPD. Activities that allow the person to brace the arms and use the accessory muscles are better tolerated. As the disease progresses, breathing becomes increasingly more labored, even at rest. The expiratory phase of respiration is prolonged, and expiratory wheezes and crackles can be heard on auscultation. People with severe airflow obstruction may also exhibit use of the accessory muscles, sitting in the characteristic "tripod" position to facilitate use of the sternocleidomastoid, scalene, and intercostal muscles.[49] Pursed-lip breathing enhances airflow because it increases the resistance to the outflow of air and helps to prevent airway collapse by increasing airway pressure. Eventually, people with COPD are unable to maintain normal blood gases by increasing their breathing effort. Hypoxemia, hypercapnia, and cyanosis develop, reflecting an imbalance between ventilation and perfusion.

Severe hypoxemia, in which arterial PO_2 levels fall below 55 mm Hg, causes reflex vasoconstriction of the pulmonary vessels and further impairment of gas exchange in the lung. It is more common in people with the chronic bronchitis form of COPD. Hypoxemia also stimulates red blood cell production, causing polycythemia. The increase in pulmonary vasoconstriction and subsequent elevation in pulmonary artery pressure further increase the work of the right ventricle. As a result, people with COPD may develop right-sided heart failure with peripheral edema (*i.e.,* cor pulmonale). However, signs of overt right-sided heart failure are seen less frequently since the advent of supplemental oxygen therapy.

Diagnosis

The diagnosis of COPD is based on a careful history and physical examination, pulmonary function studies, chest radiographs, and laboratory tests. Airway obstruction prolongs the expiratory phase of respiration and affords the

potential for impaired gas exchange because of mismatching of ventilation and perfusion. The FVC is the amount of air that can be forcibly exhaled after maximal inspiration. In an adult with normal respiratory function, this should be achieved in 4 to 6 seconds. In people with chronic lung disease, the time required for FVC is increased, the $FEV_{1.0}$ is decreased, and the ratio of $FEV_{1.0}$ to FVC is decreased. In severe disease, the FVC is markedly reduced. Lung volume measurements reveal a marked increase in RV, an increase in TLC, and elevation of the RV-to-TLC ratio. These and other measurements of expiratory flow are determined by spirometry and are used in the diagnosis of COPD. Spirometry measurements can be used in staging disease severity. For example, an $FEV_{1.0}$-to-FVC ratio of less than 70% with an $FEV_{1.0}$ of 80% or more, with or without symptoms, indicates mild disease, and an $FEV_{1.0}$-to-FVC ratio of less than 70% with an $FEV_{1.0}$ of less than 50%, with or without symptoms, indicates severe disease.[35] Other diagnostic measures become important as the disease advances. Measures of exercise tolerance, nutritional status, hemoglobin saturation, and arterial blood gases can be used to assess the overall impact of COPD on health status and to direct treatment.

Treatment

The treatment of COPD depends on the stage of the disease and often requires an interdisciplinary approach. Smoking cessation is the only measure that slows the progression of the disease. Education of people with COPD and their families is a key to successful management of the disease. Psychosocial rehabilitation must be individualized to meet the specific needs of people with COPD and their families. These needs vary with age, occupation, financial resources, social and recreational interests, and interpersonal and family relationships.

People in more advanced stages of the disease often require measures to maintain and improve physical and psychosocial functioning, pharmacologic interventions, and oxygen therapy. Avoidance of cigarette smoke and other environmental airway irritants is imperative. Wearing a cold-weather mask often prevents dyspnea and bronchospasm due to cold air and wind exposure.

Respiratory tract infections can prove life threatening to people with severe COPD. A person with COPD should avoid exposure to others with known respiratory tract infections and should avoid attending large gatherings during periods of the year when influenza or respiratory tract infections are prevalent. Immunization for influenza and pneumococcal infections decreases the likelihood of their occurrence.

Maintaining and improving physical and psychosocial functioning is an important part of the treatment program for people with COPD. A long-term pulmonary rehabilitation program can significantly reduce episodes of hospitalization and add measurably to a person's ability to manage and cope with his or her impairment in a positive way. This program includes breathing exercises that focus on restoring the function of the diaphragm, reducing the work of breathing, and improving gas exchange. Physical conditioning with appropriate exercise training increases maximal oxygen consumption and reduces ventilatory effort and heart rate for a given workload. Work simplification and energy conservation strategies may be needed when impairment is severe.

The pharmacologic treatment of COPD includes the use of bronchodilators, including inhaled adrenergic and anticholinergic agents. Inhaled β_2-adrenergic agonists have been the mainstay of treatment of COPD. It has been suggested that long-acting inhaled β_2-adrenergic agonists may be even more effective than the short-acting forms of the drug. The anticholinergic drugs (*e.g.,* ipratropium bromide, tiotropium bromide), which are administered by inhalation, produce bronchodilation by blocking parasympathetic cholinergic receptors that produce contraction of bronchial smooth muscle. These medications, which are administered by inhalation, produce bronchodilation by direct action on the large airways and do not change the composition or viscosity of the bronchial mucus. They also reduce the volume of sputum without altering its viscosity. Because these drugs have a slower onset and longer duration of action, they usually are used on a regular basis rather than on an as-needed basis. Inhalers that combine an anticholinergic drug with a β_2-adrenergic agonist are available.

Inhaled corticosteroids often are used in treatment of COPD; there is controversy regarding their usefulness. An explanation for this lack of effect may be related to the fact that corticosteroids prolong the action of neutrophils and hence do not suppress the neutrophilic inflammation seen in COPD. Because corticosteroids are useful in relieving asthma symptoms, they may benefit people with asthma concomitant with COPD. Inhaled corticosteroids also may be beneficial in treating acute exacerbations of COPD, minimizing the undesirable effects that often accompany systemic use.

Oxygen therapy is prescribed for selected people with significant hypoxemia (arterial $PO_2 < 55$ mm Hg). Administration of continuous low-flow (1 to 2 L/minute) oxygen to maintain arterial PO_2 levels between 55 and 65 mm Hg decreases dyspnea and pulmonary hypertension and improves neuropsychological function and activity tolerance. The overall goal of oxygen therapy is to maintain a hemoglobin oxygen saturation of at least 90%.[45] Because the ventilatory drive associated with hypoxic stimulation of the peripheral chemoreceptors does not occur until the arterial PO_2 has been reduced to about 60 mm Hg or less, increasing the arterial PO_2 above 60 mm Hg tends to depress the hypoxic stimulus for ventilation and often leads to hypoventilation and carbon dioxide retention.

Cystic Fibrosis

CF, which is the major cause of severe chronic respiratory disease in children, is an autosomal recessive disorder involving the exocrine glands in the epithelial lining of the respiratory, gastrointestinal, and reproductive tracts.[39] CF affects about 30,000 children and adults in the United States and more than

10 million persons are asymptomatic carriers of the defective gene.[39] The defective gene, cystic fibrosis transmembrane regulator (CFTR), and its protein product cause excessive thick mucus that obstructs lungs and the pancreas. In addition to chronic respiratory disease, CF is manifested by pancreatic exocrine deficiency and elevation of sodium chloride in the sweat. Nasal polyps, sinus infections, pancreatitis, and cholelithiasis also are seen with CF. Most boys with CF have congenital bilateral absence of the vas deferens with azoospermia.

Etiology and Pathogenesis

CF is caused by mutations in a single gene on the long arm of chromosome 7 that encodes for the CFTR, which functions as a chloride (Cl^-) channel in epithelial cell membranes. Mutations in the CFTR gene render the epithelial membrane relatively impermeable to the chloride ion (Fig. 37.14).

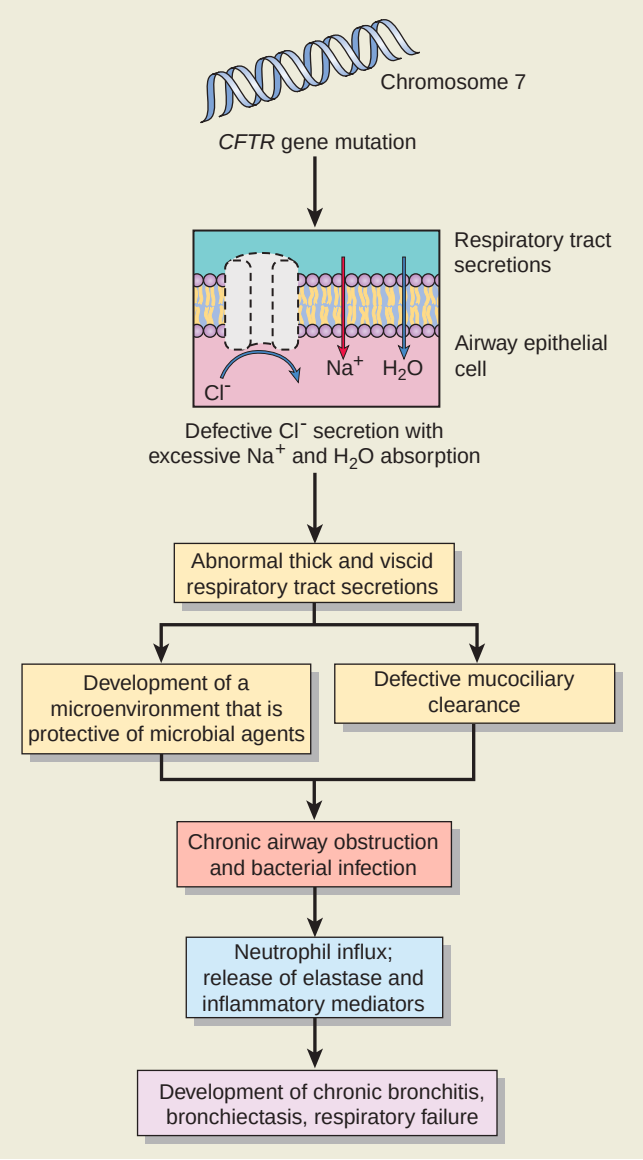


FIGURE 37.14 • Pathogenesis of cystic fibrosis.

There are greater than 1000 possible CTFR changes that can occur. However, 70% of CF individuals have F 508, which is a deletion of 3 bases that cause the loss of phenylalanine and a more severe phenotype.[40] Others have a partial loss of CTFR so their phenotype is less severe and often goes unnoticed until they have an acute injury such as pneumonia and may need intubation and mechanical ventilation.

The impact on impaired Cl^- transport is relatively tissue specific. In the sweat glands, the concentration of sodium (Na^+) and Cl^- secreted into the lumen of the gland remains unaffected, whereas the reabsorption of Cl^- through the CFTR and accompanying reabsorption of Na^+ in the ducts of the gland fail to occur. This defect accounts for the high concentration of NaCl in the sweat of persons with CF.[40] In the normal airway epithelium, Cl^- is secreted into airway lumen through the CFTR. The impaired transport of Cl^- ultimately leads to a series of secondary events, including increased absorption of Na^+ and water from the airways into the blood. This lowers the water content of the mucociliary blanket coating the respiratory epithelium, causing it to become more viscid. The resulting dehydration of the mucous layer leads to defective mucociliary function and accumulation of viscid secretions that obstruct the airways and predispose to recurrent pulmonary infections. Similar transport abnormalities and pathophysiologic events take place in the pancreatic and biliary ducts and in the vas deferens in boys.

Clinical Manifestations

Respiratory manifestations of CF are caused by an accumulation of viscid mucus in the bronchi, impaired mucociliary clearance, and lung infections. Chronic bronchiolitis and bronchitis are the initial lung manifestations. However, after months and years, structural changes in the bronchial wall lead to bronchiectasis. In addition to airway obstruction, the basic genetic defect that occurs with CF predisposes to chronic infection with a surprisingly limited number of organisms, the most common being *Pseudomonas aeruginosa*.[40] Soon after birth, initial infection with bacterial pathogens occurs and is associated with an excessive neutrophilic inflammatory response that appears to be independent of the infection itself. There is evidence that the CF airway epithelial cells or surface liquids provide a favorable environment for harboring these organisms. *P. aeruginosa,* in particular, has a propensity to undergo mucoid transformation in this environment.[40] The complex polysaccharide produced by these organisms provides a hypoxic environment and generates a biofilm that protects *Pseudomonas* against antimicrobial agents. Pulmonary inflammation is another cause of decline in respiratory function in people with CF and may precede the onset of chronic infection.

Pancreatic function is often abnormal to some degree with individuals with CF. Steatorrhea, diarrhea, and abdominal pain and discomfort are common. In the newborn, meconium ileus may cause intestinal obstruction, a fatal condition if left untreated. The degree of pancreatic involvement is highly variable. In some children, the defect is relatively mild,

and in others, the involvement is severe and impairs intestinal absorption. In addition to exocrine pancreatic insufficiency, hyperglycemia may occur, especially after 10 years of age, when many people with CF develop diabetes mellitus.[39]

Diagnosis and Treatment

Early diagnosis and treatment are important in delaying the onset and severity of chronic illness in children with CF. Diagnosis is based on the presence of respiratory and gastrointestinal manifestations typical of CF, a history of CF in a sibling, or a positive newborn screening test result. Confirmatory laboratory tests include the sweat test, assessment of bioelectrical properties of respiratory epithelia in the nasal membrane, and genetic tests for *CFTR* gene mutations. The *sweat test,* using pilocarpine iontophoresis to collect the sweat followed by chemical analysis of its chloride content, remains the standard approach to diagnosis. Newborns with CF have elevated blood levels of immunoreactive trypsinogen, presumably because of secretory obstruction in the pancreas. *Newborn screening* consists of a test for determination of immunoreactive trypsinogen.

Twenty years after cloning the CFTR gene, there are still no approved treatments for correcting the genetic defects in CF or to reverse the ion transport abnormalities associated with the dysfunctional CFTR. Drugs focused at the CFTR gene are known as protein repair therapy and are being trialed and predicted to be of use in the future.[41] Thus, treatment measures are directed toward slowing the progression of secondary organ dysfunction and sequelae such as chronic lung infection and pancreatic insufficiency.[41] They include the use of antibiotics to prevent and manage infections, the use of chest physical therapy (chest percussion and postural drainage) and mucolytic agents to prevent airway obstruction, and pancreatic enzyme replacement, and nutritional therapy.

Appropriate antibiotic therapy directed against bacterial pathogens isolated from the respiratory tract is an essential component in the management of CF lung disease. Indications for oral antibiotics include the presence of respiratory tract symptoms and identification of pathogenic organisms in respiratory tract cultures. Intravenous antibiotics are used for progressive and unrelenting symptoms.

People with CF who have complete loss of exocrine pancreas function and have inadequate digestion of fats and proteins require diet adjustment, pancreatic enzyme replacement, and supplemental vitamins and minerals. Many people with CF have a higher-than-normal caloric need because of the increased work of breathing and perhaps because of the increased metabolic activity related to the basic defect. Pancreatic enzyme dosage and product type are individualized for each person.

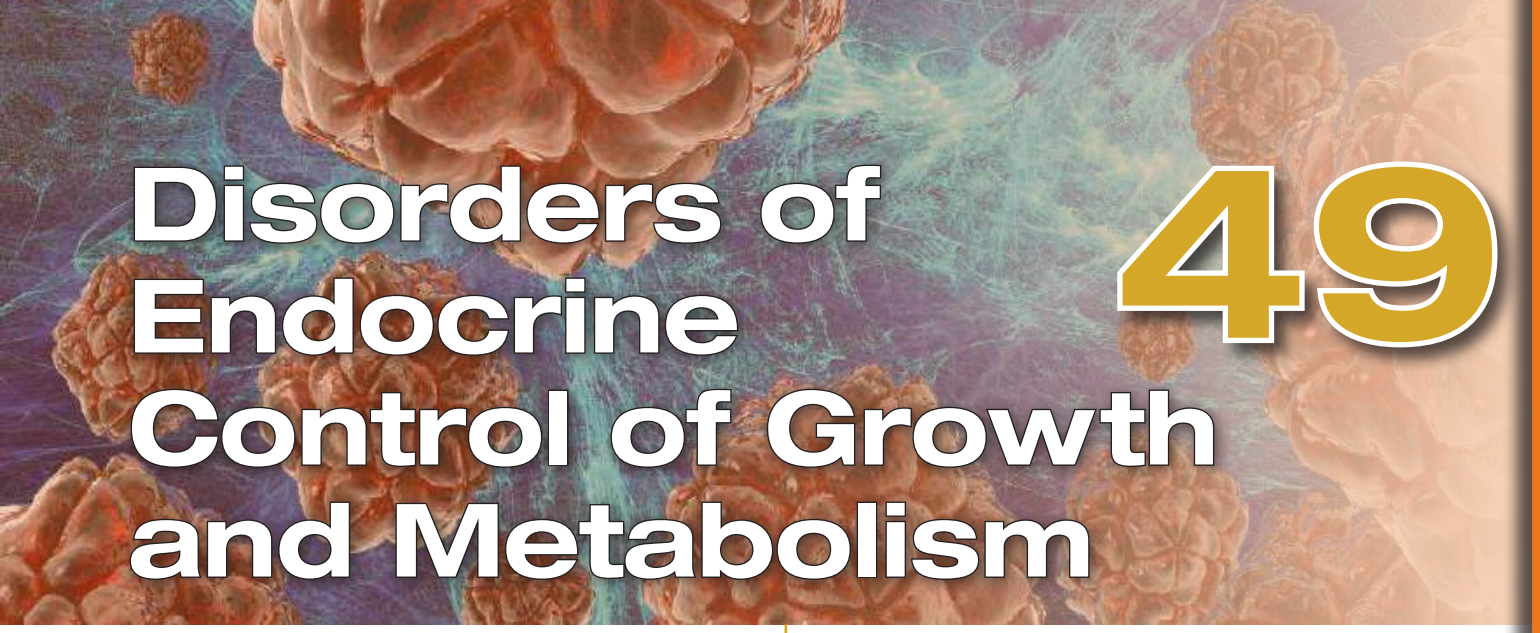
Progress of the disease is variable. Improved medical management has led to longer survival. Today, many people with the disease can expect to live into their 30s, 40s, and beyond.[39] Lung transplantation is being used as a treatment for people with end-stage lung disease. Current hopes reside in research that would make gene therapy a feasible alternative for people with the disease.

IN SUMMARY

Obstructive ventilatory disorders are characterized by airway obstruction and limitation in expiratory airflow. Asthma is a chronic inflammatory disorder of the airways characterized by airway hyperreactivity, airway narrowing, and airway remodeling. T_1H cells differentiate in response to microbes and stimulate the differentiation of B cells into immunoglobulin (Ig)M– and IgG-producing plasma cells. Whereas, T_2H cells respond to allergens by stimulating B cells to differentiate into IgE-producing plasma cells, produce growth factors for mast cells, and recruit and activate eosinophils. In people with allergic asthma, T-cell differentiation appears to be skewed toward a pro-inflammatory T_2H response. It appears that both genetic and environmental factors play a role in the development of asthma or reactive airway disease.

COPD describes a group of conditions characterized by obstruction to airflow in the lungs. Among the conditions associated with COPD are emphysema, chronic bronchitis, and bronchiectasis. Emphysema is characterized by a loss of lung elasticity, abnormal, permanent enlargement of the airspaces distal to the terminal bronchioles, and hyperinflation of the lungs. Chronic bronchitis is caused by inflammation of major and small airways and is characterized by edema and hyperplasia of submucosal glands and excess mucus secretion into the bronchial tree. A history of a chronic productive cough that has persisted for at least 3 months and for at least 2 consecutive years in the absence of other disease is necessary for the diagnosis of chronic bronchitis. Emphysema and chronic bronchitis are manifested by eventual mismatching of ventilation and perfusion. As the condition advances, signs of respiratory distress and impaired gas exchange become evident, with development of hypercapnia and hypoxemia. Bronchiectasis is a less common form of COPD that is characterized by an abnormal dilation of the large bronchi associated with infection and destruction of the bronchial walls.

CF is an autosomal recessive genetic disorder manifested by chronic lung disease, pancreatic exocrine deficiency, and elevation of sodium chloride in the sweat. The disorder is caused by a mutation of a single gene on the long arm of chromosome 7 that codes for the CFTR, which functions in the transepithelial transport of the chloride ion. The defect causes exocrine gland secretions to become exceedingly viscid, and it promotes colonization of the respiratory tract with *P. aeruginosa* and other organisms such as *Staphylococcus aureus*. Accumulation of viscid mucus in the bronchi, impaired mucociliary function, and infection contribute to the development of chronic lung disease and a decreased life expectancy.



49 Disorders of Endocrine Control of Growth and Metabolism

Sheila Grossman

The endocrine system affects all aspects of body function, including growth and development, energy metabolism, muscle and adipose tissue distribution, sexual development, fluid and electrolyte balance, and inflammation and immune responses. This chapter focuses on disorders of pituitary function, growth and growth hormone, thyroid function, and adrenal cortical function.

THYROID DISORDERS

After completing this section of the chapter, you should be able to meet the following objectives:

- Characterize the synthesis, transport, and regulation of thyroid hormone.
- Describe tests in the diagnosis and management of thyroid disorders.

Control of Thyroid Function

The thyroid gland is a shield-shaped structure located immediately below the larynx in the anterior middle portion of the neck (Fig. 49.3A). It is composed of a large number of tiny, saclike structures called *follicles* (see Fig. 49.3B). These are the functional units of the thyroid. Each follicle is formed by a single layer of epithelial (follicular) cells and is filled with a secretory substance called *colloid,* which consists largely of a glycoprotein–iodine complex called *thyroglobulin*.[2]

The thyroglobulin that fills the thyroid follicles is a large glycoprotein molecule that contains 140 tyrosine amino acids. In the process of thyroid synthesis, iodine is attached to these tyrosine molecules. Both thyroglobulin and iodide are secreted into the colloid of the follicle by the follicular cells.[2]

The thyroid is remarkably efficient in its use of iodide. A daily absorption of approximately 50 mg of ingested iodine or about 1 mg/week is necessary to form normal quantities of thyroid hormone.[4] In the process of removing it from the blood and storing it for future use, iodide is pumped into the follicular cells against a concentration gradient. Iodide (I^-) is transported across the basement membrane of the thyroid cells by an intrinsic membrane protein called the *Na^+/I symporter* (NIS).[4] At the apical border, a second I^- transport protein called *pendrin* moves iodine into the colloid, where it is involved in hormonogenesis.[4] The NIS derives its energy from Na^+/K^+-ATPase, which drives the process. As a result, the concentration of iodide in the normal thyroid gland is approximately 40 times that in the blood.[2]

The NIS is stimulated by both TSH and the TSH receptor–stimulating antibody found in Graves disease. Pendrin, encoded by the Pendred syndrome gene (*PDS*), is a transporter of chloride and iodide. Mutations in the *PDS* gene have been found in patients with goiter and congenital deafness.[2]

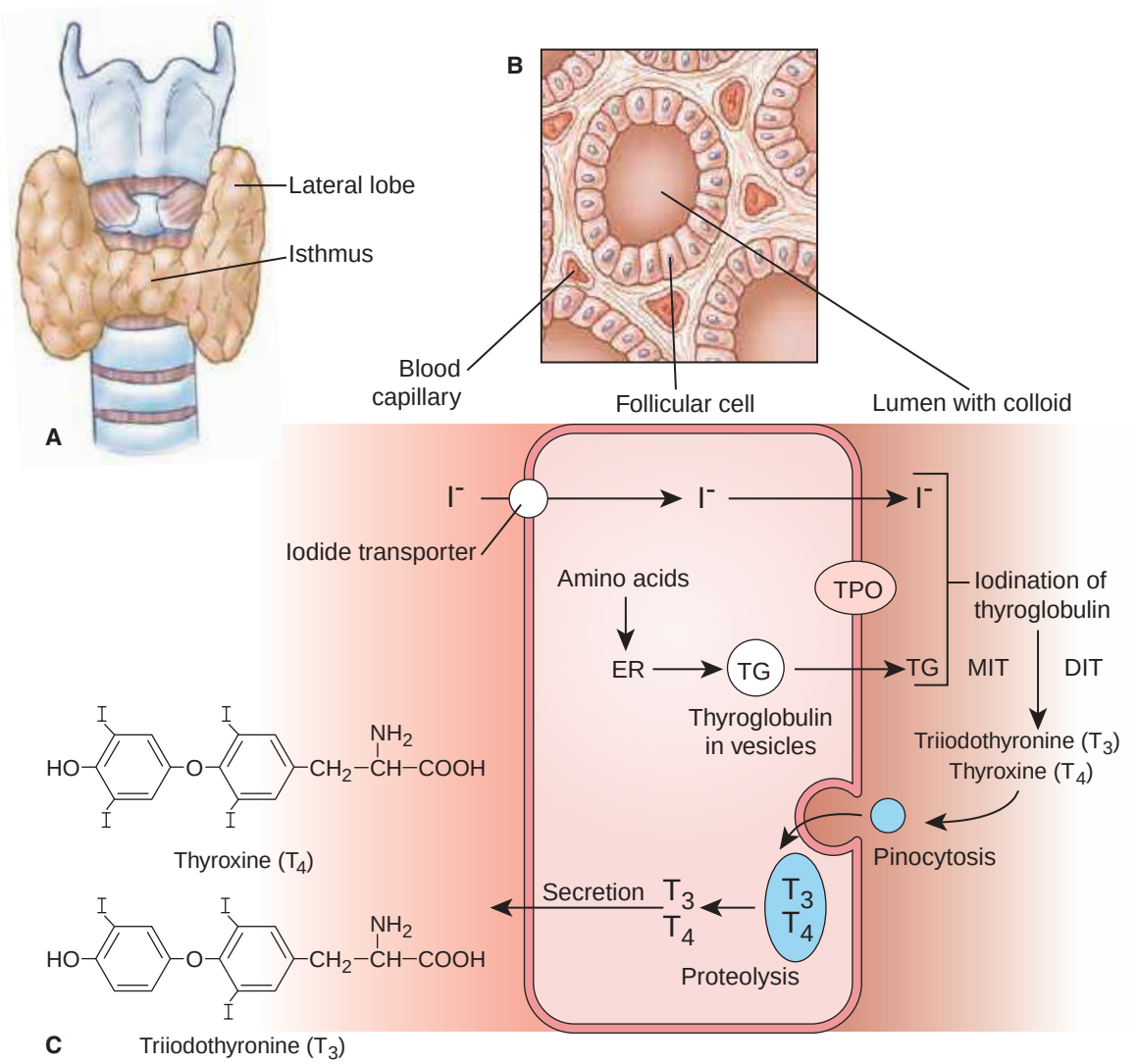


FIGURE 49.3 • (**A**) The thyroid gland. (**B**) Microscopic structure of thyroid follicles. (**C**) Cellular mechanisms for transport of iodide (I^-), oxidation of I^- by thyroperoxidase (TPO), coupling of oxidized I^- with thyroglobulin to form thyroid hormones, and movement of T_3 and T_4 into the follicular cell by pinocytosis and release into the blood.

Once inside the follicle, most of the iodide is oxidized by the enzyme thyroid peroxidase (TPO) in a reaction that facilitates combination with a tyrosine molecule to form monoiodotyrosine (MIT) and then diiodotyrosine (DIT).[4] Two DIT residues are coupled to form thyroxine (T_4), or a MIT and a DIT are coupled to form triiodothyronine (T_3).[2] Only T_4 (90%) and T_3 (10%) are released into the circulation (see Fig. 49.3C). There is evidence that T_3 is the active form of the hormone and that T_4 is converted to T_3 before it can act physiologically.

Thyroid hormones are bound to thyroxine-binding globulin (TBG) and other plasma proteins for transport in the blood. Only the free hormone enters cells and regulates the pituitary feedback mechanism. Protein-bound thyroid hormone forms a large reservoir that is slowly drawn on as free thyroid hormone is needed. There are three major thyroid-binding proteins: TBG, transthyretin (formerly known as thyroxine-binding prealbumin [TBPA]), and albumin. More than 99% of T_4 and T_3 is carried in the bound form.[2] TBG carries approximately 70% of T_4 and T_3; transthyretin binds approximately 10% of circulating T_4 and lesser amounts of T_3; and albumin binds approximately 15% of circulating T_4 and T_3.[2]

A number of disease conditions and pharmacologic agents can decrease the amount of binding protein in the plasma or influence the binding of hormone. Congenital TBG deficiency is an X-linked trait that occurs in 1 of every 5000 live births.[2] Premature sick infants need to be screened with a comprehensive thyroid serum profile in order to prevent missing primary hypothyroidism on infants.[17] Glucocorticoid medications and systemic disease conditions such as protein malnutrition, nephrotic syndrome, and cirrhosis decrease TBG concentrations. Medications such as phenytoin, salicylates, and diazepam can affect the binding of thyroid hormone to normal concentrations of binding proteins.

The secretion of thyroid hormone is regulated by the hypothalamic–pituitary–thyroid feedback system (Fig. 49.4). In this system, thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus, controls the release of TSH from the anterior pituitary gland. TSH increases the overall activity of the thyroid gland by increasing thyroglobulin breakdown and the release of thyroid hormone from follicles into the bloodstream, activating the iodide pump (by increasing NIS activity), increasing the oxidation of iodide and the coupling of iodide to tyrosine, and increasing the number and the size of the follicle cells. The effect of TSH on the release of thyroid hormones occurs within approximately 30 minutes, but the other effects require days or weeks.

Increased levels of thyroid hormone act in the feedback inhibition of TRH or TSH. High levels of iodide also cause a temporary decrease in thyroid activity that lasts for several weeks, probably through a direct inhibition of TSH on the thyroid.[4] Cold exposure is one of the strongest stimuli for increased thyroid hormone production and probably is mediated through TRH from the hypothalamus. Various emotional reactions can also affect the output of TRH and TSH.

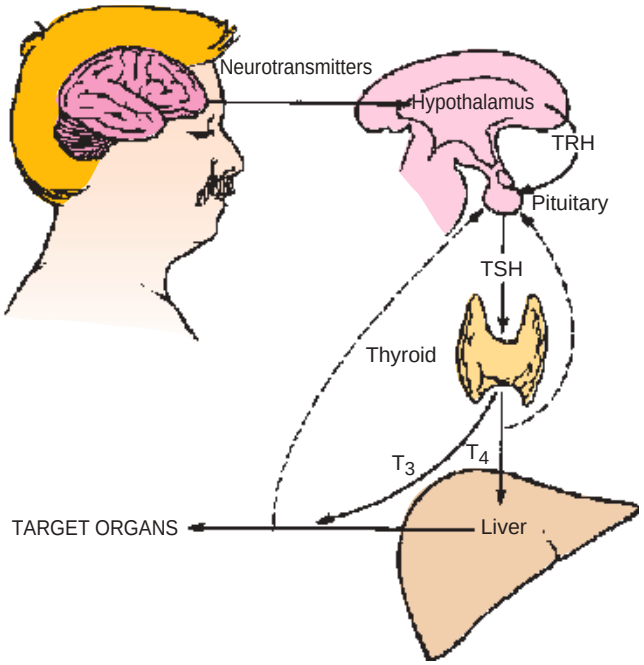


FIGURE 49.4 • The hypothalamic–pituitary–thyroid feedback axis. (From Morton P. G., Fontaine D. K. (2009). *Critical care nursing: A holistic approach* (9th ed., p. 1111). Philadelphia, PA: Lippincott Williams & Wilkins.)

Actions of Thyroid Hormone

Altered levels of thyroid hormone affect all the major organs in the body. Thyroid hormone has two major functions—it increases metabolism and protein synthesis, and it is necessary for growth and development in children, including mental development and attainment of sexual maturity. These actions are mainly mediated by T_3. In the cell, T_3 binds to a nuclear receptor, resulting in transcription of specific thyroid hormone response genes.[2]

Metabolic Rate. Thyroid hormone increases the metabolism of all body tissues except the retinas, spleen, testes, and lungs. The basal metabolic rate can increase by 60% to 100% above normal when large amounts of T_4 are present.[2] As a result of this higher metabolism, the rate of glucose, fat, and protein use increases. Lipids are mobilized from adipose tissue, and the catabolism of cholesterol by the liver is increased. Blood levels of cholesterol are decreased in hyperthyroidism and increased in hypothyroidism.[2] Muscle proteins are broken down and used as fuel, probably accounting for some of the muscle fatigue that occurs with hyperthyroidism. The absorption of glucose from the gastrointestinal tract is increased.

Cardiovascular Function. Cardiovascular and respiratory functions are strongly affected by thyroid function. With an increase in metabolism, there is a rise in oxygen consumption and production of metabolic end products, with an accompanying increase in vasodilation. Blood flow to the skin, in particular, is augmented as a means of dissipating the body heat that results from the higher metabolic rate. Blood volume,

cardiac output, and ventilation are all increased as a means of maintaining blood flow and oxygen delivery to body tissues. Heart rate and cardiac contractility are enhanced as a means of maintaining the needed cardiac output. Blood pressure is likely to change little because the increase in vasodilation tends to offset the increase in cardiac output.

Gastrointestinal Function. Thyroid hormone enhances gastrointestinal function, causing an increase in motility and production of gastrointestinal secretions that often results in diarrhea. An increase in appetite and food intake accompanies the higher metabolic rate that occurs with increased thyroid hormone levels. At the same time, weight loss occurs because of the increased use of calories.

Neuromuscular Effects. Thyroid hormone has marked effects on neural control of muscle function and tone. Slight elevations in hormone levels cause skeletal muscles to react more vigorously, and a drop in hormone levels causes muscles to react more sluggishly. In the hyperthyroid state, a fine muscle tremor is present. The cause of this tremor is unknown, but it may represent an increased sensitivity of the neural synapses in the spinal cord that control muscle tone. In the infant, thyroid hormone is necessary for normal brain development. The hormone enhances cerebration; in the hyperthyroid state, it causes extreme nervousness, anxiety, and difficulty in sleeping.

Evidence suggests a strong interaction between thyroid hormone and the sympathetic nervous system.[4] Many of the signs and symptoms of hyperthyroidism suggest overactivity of the sympathetic division of the autonomic nervous system, such as tachycardia, palpitations, and sweating. Tremor, restlessness, anxiety, and diarrhea may also reflect autonomic nervous system imbalances. Drugs that block sympathetic activity have proved to be valuable adjuncts in the treatment of hyperthyroidism because of their ability to relieve some of these undesirable symptoms.[18]

KEY POINTS

THYROID HORMONE

- Thyroid hormone increases the metabolism and protein synthesis in nearly all of the tissues of the body.
- When hypothyroidism occurs in older children or adults, it produces a decrease in metabolic rate, an accumulation of a hydrophilic mucopolysaccharide substance (myxedema) in the connective tissues throughout the body, and an elevation in serum cholesterol.
- Hyperthyroidism has an effect opposite that of hypothyroidism. It produces an increase in metabolic rate and oxygen consumption, increased use of metabolic fuels, and increased sympathetic nervous system responsiveness.

Tests of Thyroid Function

Various tests aid in the diagnosis of thyroid disorders.[19] Measures of T_3, T_4, and TSH have been made available through immunoassay methods. The free T_4 test measures the unbound portion of T_4 that is free to enter cells to produce its effects and is most often the first laboratory value obtained. TSH levels are used to differentiate between primary and secondary thyroid disorders. T_3, T_4, and free T_4 levels are low in primary hypothyroidism, and the TSH level is elevated (see Fig. 49.4). The assessment of thyroid autoantibodies (*e.g.,* anti-TPO antibodies in Hashimoto thyroiditis) is important in the diagnostic workup and consequent follow-up of people with thyroid disorders.

The radioiodine (^{123}I) uptake test measures the ability of the thyroid gland to concentrate and retain iodine from the blood.[11] Thyroid scans (^{123}I, ^{99m}Tc-pertechnetate) can be used to detect thyroid nodules and determine the functional activity of the thyroid gland. Ultrasonography can be used to differentiate cystic from solid thyroid lesions, and CT and MRI scans are used to demonstrate tracheal compression or impingement on other neighboring structures. Fine-needle aspiration biopsy of a thyroid nodule has proved to be the best method for differentiation of benign from malignant thyroid disease.

Alterations in Thyroid Function

An alteration in thyroid function can represent a hypofunctional or a hyperfunctional state. The manifestations of these two altered states are summarized in Table 49.3. Disorders of the thyroid may be due to a congenital defect in thyroid development, or they may develop later in life, with a gradual or sudden onset.

Goiter is an increase in the size of the thyroid gland (Fig. 49.5). It can occur in hypothyroid, euthyroid, and hyperthyroid states. Goiters may be diffuse, involving the entire gland without evidence of nodularity, or they may contain nodules. Diffuse goiters usually become nodular. Goiters may be toxic, producing signs of extreme hyperthyroidism, or thyrotoxicosis, or they may be nontoxic. Diffuse nontoxic and multinodular goiters are the result of compensatory hypertrophy and hyperplasia of follicular epithelium from some derangement that impairs thyroid hormone output.

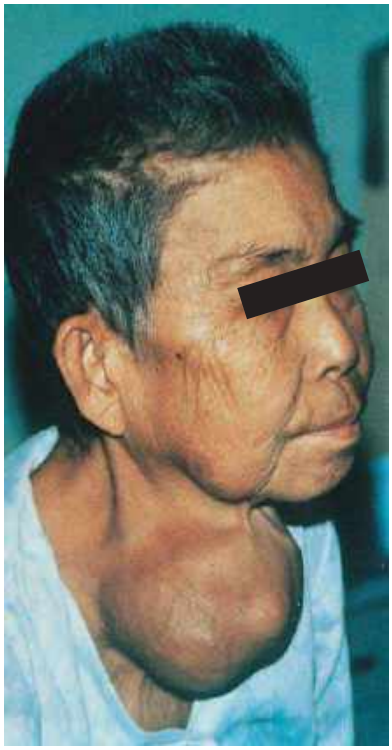
The degree of thyroid enlargement is usually proportional to the extent and duration of thyroid deficiency. Multinodular goiters produce the largest thyroid enlargements. When sufficiently enlarged, they may compress the esophagus and trachea, causing difficulty in swallowing, a choking sensation, and inspiratory stridor. Such lesions may also compress the superior vena cava, producing distention of the veins of the neck and upper extremities, edema of the eyelids and conjunctiva, and syncope with coughing.

Hypothyroidism

Hypothyroidism can occur as a congenital or an acquired defect. Congenital hypothyroidism develops prenatally and is present at birth. Acquired hypothyroidism develops because

TABLE 49.3 MANIFESTATIONS OF HYPOTHYROID AND HYPERTHYROID STATES

LEVEL OF ORGANIZATION	HYPOTHYROIDISM	HYPERTHYROIDISM
Basal metabolic rate	Decreased	Increased
Sensitivity to catecholamines	Decreased	Increased
General features	Myxedematous features	Exophthalmos (in Graves disease)
	Deep voice	Lid lag
	Impaired growth (child)	Accelerated growth (child)
Blood cholesterol levels	Increased	Decreased
General behavior	Mental retardation (infant)	Restlessness, irritability, anxiety
	Mental and physical sluggishness	Hyperkinesis
	Somnolence	Wakefulness
Cardiovascular function	Decreased cardiac output	Increased cardiac output
	Bradycardia	Tachycardia and palpitations
Gastrointestinal function	Constipation	Diarrhea
	Decreased appetite	Increased appetite
Respiratory function	Hypoventilation	Dyspnea
Muscle tone and reflexes	Decreased	Increased, with tremor and twitching
Temperature tolerance	Cold intolerance	Heat intolerance
Skin and hair	Decreased sweating	Increased sweating
	Coarse and dry skin and hair	Thin and silky skin and hair
Weight	Gain	Loss



Goiter

FIGURE 49.5 • Goiter illustrates an enlarged thyroid gland. (From Rubin R., Strayer D. (2012). *Pathology: Clinicopathologic Foundations of Medicine*. (6th ed., p. 1047, Figure 21.11A). Philadelphia, PA: Lippincott Williams & Wilkins.)

of primary disease of the thyroid gland or secondary to disorders of hypothalamic or pituitary origin.

Congenital Hypothyroidism

Congenital hypothyroidism is a common cause of preventable mental retardation. It affects approximately 1 in 4000 infants. Hypothyroidism in the infant may result from a congenital lack of the thyroid gland or from abnormal biosynthesis of thyroid hormone or deficient TSH secretion. With congenital lack of the thyroid gland, the infant usually appears normal and functions normally at birth because hormones have been supplied in utero by the mother.

Thyroid hormone is essential for normal growth and brain development, almost half of which occurs during the first 6 months of life.[17] If untreated, congenital hypothyroidism causes mental retardation and impairs physical growth. The manifestations of untreated congenital hypothyroidism are referred to as cretinism. However, the term does not apply to the normally developing infant in whom replacement thyroid hormone therapy was instituted shortly after birth.

Fortunately, neonatal screening tests have been instituted to detect congenital hypothyroidism during early infancy.[17] Screening is usually done in the hospital nursery. In this test, a drop of blood is taken from the infant's heel and analyzed for T_4 and TSH.

Transient congenital hypothyroidism has been recognized more frequently since the introduction of neonatal screening. High TSH levels and low or normal thyroid hormone levels characterize it. The fetal and infant thyroids are

sensitive to iodine excess. Iodine crosses the placenta and mammary glands and is readily absorbed by infant skin. Transient hypothyroidism may be caused by maternal or infant exposure to substances such as povidone–iodine used as a disinfectant (*i.e.,* vaginal douche or skin disinfectant in the nursery). Antithyroid drugs such as propylthiouracil and methimazole can cross the placenta and block fetal thyroid function.[17]

Congenital hypothyroidism is treated by hormone replacement. Evidence indicates that it is important to normalize T_4 levels as rapidly as possible because a delay is accompanied by poorer psychomotor and mental development.[17] Dosage levels are adjusted as the child grows. When early and adequate treatment regimens are followed, the risk of mental retardation in infants detected by screening programs is essentially nonexistent.

Acquired Hypothyroidism and Myxedema

Hypothyroidism in older children and adults causes a general slowing down of metabolic processes and myxedema. Myxedema implies the presence of a nonpitting mucus type of edema caused by an accumulation of a hydrophilic mucopolysaccharide substance in the connective tissues throughout the body.[2] The hypothyroid state may be mild, with only a few signs and symptoms, or it may progress to a life-threatening condition with angioedema.[20]

Etiology and Pathogenesis. Acquired hypothyroidism can result from destruction or dysfunction of the thyroid gland (*i.e.,* primary hypothyroidism), or it can be a secondary disorder caused by impaired pituitary function or as a tertiary disorder caused by a hypothalamic dysfunction.

Primary hypothyroidism is much more common than secondary (and tertiary) hypothyroidism. It may result from thyroidectomy (*i.e.,* surgical removal) or ablation of the gland with radiation. Certain goitrogenic agents, such as lithium carbonate (used in the treatment of manic-depressive states), and the antithyroid drugs propylthiouracil and methimazole in continuous dosage can block hormone synthesis and produce hypothyroidism with goiter. Large amounts of iodine (*i.e.,* ingestion of kelp tablets or iodide-containing cough syrups, or administration of iodide-containing radiographic contrast media or the cardiac antiarrhythmic class III drug amiodarone, which contains 75 mg of iodine per 200-mg tablet) can also block thyroid hormone production and cause goiter, particularly in persons with autoimmune thyroid disease.[21] Iodine deficiency, which can cause goiter and hypothyroidism, is uncommon in the United States because of the widespread use of iodized salt and other iodide sources. However, iodine deficiency affects an estimated 100 million people worldwide.

The most common cause of hypothyroidism is Hashimoto thyroiditis, an autoimmune disorder in which the thyroid gland may be totally destroyed by an immunologic process.[2] It is the major cause of goiter and hypothyroidism in children and adults. Hashimoto thyroiditis is predominantly a disease of women. The course of the disease varies. At the onset, only a goiter may be present. In time, hypothyroidism usually becomes evident. Although the disorder usually causes hypothyroidism, a hyperthyroid state may develop midcourse in the disease. The transient hyperthyroid state is caused by leakage of preformed thyroid hormone from damaged cells of the gland.[22] Subacute thyroiditis, which can occur in postpartum (postpartum thyroiditis), can also result in hypothyroidism.

Clinical Manifestations. Hypothyroidism may affect almost all body functions. The manifestations of the disorder are related largely to two factors: the hypometabolic state resulting from thyroid hormone deficiency and myxedematous involvement of body tissues. The hypometabolic state associated with hypothyroidism is characterized by a gradual onset of weakness and fatigue, a tendency to gain weight despite a loss of appetite, and cold intolerance (Fig. 49.6).[22]

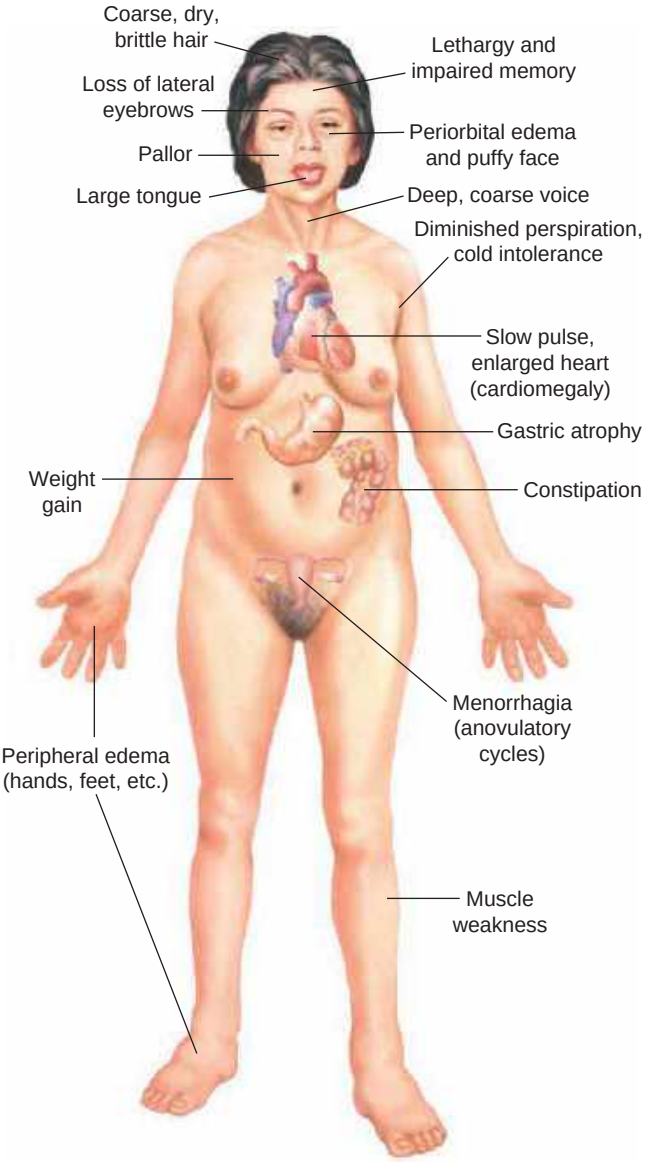


FIGURE 49.6 • Clinical manifestations of hypothyroidism.

As the condition progresses, the skin becomes dry and rough and the hair becomes coarse and brittle. The face becomes puffy with edematous eyelids, and there is thinning of the outer third of the eyebrows.[4] Gastrointestinal motility is decreased, producing constipation, flatulence, and abdominal distention. Delayed relaxation of deep tendon reflexes and bradycardia are sometimes noted. CNS involvement is manifested in mental dullness, lethargy, and impaired memory.[2,22]

Although the myxedemous fluid is usually most obvious in the face, it can collect in the interstitial spaces of almost any body structure and is responsible for many of the manifestations of the severe hypothyroid state. The tongue is often enlarged, and the voice becomes hoarse and husky. Carpal tunnel and other entrapment syndromes are common, as is impairment of muscle function with stiffness, cramps, and pain.[22] Mucopolysaccharide deposits in the heart cause generalized cardiac dilation, bradycardia, and other signs of altered cardiac function. The signs and symptoms of hypothyroidism are summarized in Table 49.3.

Diagnosis and Treatment. Diagnosis of hypothyroidism is based on history, physical examination, and laboratory tests. A low serum T_4 and elevated TSH levels are characteristic of primary hypothyroidism. The tests for antithyroid antibodies should be done when Hashimoto thyroiditis is suspected (anti-TPO antibody titers are tested frequently).[11]

Hypothyroidism is treated by replacement therapy with synthetic preparations of T_3 or T_4. Most people are treated with T_4. Serum TSH levels are used to estimate the adequacy of T_4 replacement therapy. When the TSH level is normalized, the T_4 dosage is considered satisfactory (for primary hypothyroidism only).[22] A "go low and go slow" approach should be considered in the treatment of elderly with hypothyroidism because of the risk of inducing acute coronary syndromes in the susceptible individual. It is also important that people consistently take the form of T_4 prescribed so that their laboratory values are the most representative of their thyroid state. So people should remain on generic forms of T_4 and, similarly, if people are put on brand names of T_4 they should stay on the same drug.

Myxedematous Coma

Myxedematous coma is a life-threatening, end-stage expression of hypothyroidism. It is characterized by coma, hypothermia, cardiovascular collapse, hypoventilation, and severe metabolic disorders that include hyponatremia, hypoglycemia, and lactic acidosis. The pathophysiology of myxedema coma involves three major aspects: (1) carbon dioxide retention and hypoxia, (2) fluid and electrolyte imbalance, and (3) hypothermia.[20] The severely hypothyroid person is unable to metabolize sedatives, analgesics, and anesthetic drugs, and buildup of these agents may precipitate coma.

Treatment includes aggressive management of precipitating factors; supportive therapy such as management of cardiorespiratory status, hyponatremia, and hypoglycemia; and thyroid replacement therapy. If hypothermia is present, active rewarming of the body is contraindicated because it may induce vasodilation and vascular collapse. Prevention is preferable to treatment and entails special attention to high-risk populations, such as women with a history of Hashimoto thyroiditis. These persons should be informed about the signs and symptoms of severe hypothyroidism and the need for early medical treatment.

Hyperthyroidism

Thyrotoxicosis is the clinical syndrome that results when tissues are exposed to high levels of circulating thyroid hormone.[2,4]

Etiology and Pathogenesis

In most instances, thyrotoxicosis is due to hyperactivity of the thyroid gland, or hyperthyroidism.[2] The most common cause of hyperthyroidism is Graves disease, which is accompanied by ophthalmopathy (or dermopathy) and diffuse goiter.[22] Other causes of hyperthyroidism are multinodular goiter, adenoma of the thyroid, and thyroiditis.[22] Iodine-containing agents can induce hyperthyroidism as well as hypothyroidism. Thyroid crisis, or storm, is an acutely exaggerated manifestation of the thyrotoxic state.

Clinical Manifestations

Many of the manifestations of hyperthyroidism are related to the increase in oxygen consumption and use of metabolic fuels associated with the hypermetabolic state, as well as to the increase in sympathetic nervous system activity that occurs.[18] The fact that many of the signs and symptoms of hyperthyroidism resemble those of excessive sympathetic nervous system activity suggests that thyroid hormone may heighten the sensitivity of the body to the catecholamines or that it may act as a pseudocatecholamine. With the hypermetabolic state, there are frequent complaints of nervousness, irritability, and fatigability (Fig. 49.7). Weight loss is common despite a large appetite. Other manifestations include tachycardia, palpitations, shortness of breath, excessive sweating, muscle cramps, and heat intolerance. The person appears restless and has a fine muscle tremor. Even in people without exophthalmos (*i.e.,* bulging of the eyeballs seen in ophthalmopathy), there is an abnormal retraction of the eyelids and infrequent blinking such that they appear to be staring. The hair and skin are usually thin and have a silky appearance. About 15% of older adults with new-onset atrial fibrillation have thyrotoxicosis.[2] The signs and symptoms of hyperthyroidism are summarized in Table 49.3.

The treatment of hyperthyroidism is directed toward reducing the level of thyroid hormone. This can be accomplished with eradication of the thyroid gland with radioactive iodine, through surgical removal of part or all of the gland, or the use of drugs that decrease thyroid function and thereby the effect of thyroid hormone on the peripheral

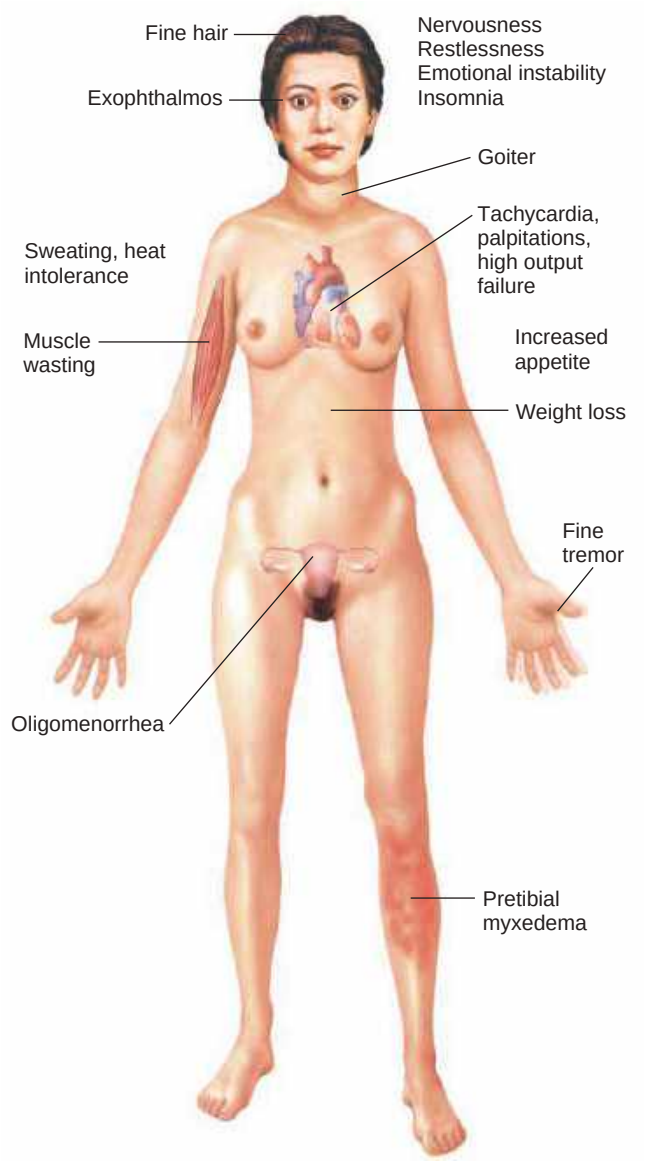


FIGURE 49.7 • Clinical manifestations of hyperthyroidism.

tissues. Eradication of the thyroid with radioactive iodine is more frequently undertaken than surgery. The β-adrenergic blocking drugs (propranolol, metoprolol, atenolol, and nadolol are preferred) are administered to block the effects of the hyperthyroid state on sympathetic nervous system function. They are given in conjunction with antithyroid drugs such as propylthiouracil and methimazole. These drugs prevent the thyroid gland from converting iodine to its organic (hormonal) form and block the conversion of T_4 to T_3 in the tissues (propylthiouracil only).[22]

Graves Disease

Graves disease is a state of hyperthyroidism, goiter, and ophthalmopathy. Onset is usually between the ages of 20 and 40 years. It affects approximately 0.5% to 1% of the population under 40 years of age.[23] Graves disease is an autoimmune disorder characterized by abnormal stimulation of the thyroid gland by thyroid-stimulating antibodies (TSH receptor antibodies) that act through the normal TSH receptors. It may be associated with other autoimmune disorders such as myasthenia gravis. The disease is associated with a major histocompatibility complex class 1 chain–related gene A (MICA), with genotypes MICA A5 correlated with Graves disease and MICA A6/A9 being preventive for Graves disease.[23]

The ophthalmopathy, which occurs in up to one third of people with Graves disease, is thought to result from accumulation of T lymphocytes sensitized to antigens along thyroid follicular cells and orbital fibroblasts that secrete cytokines.[23] The ophthalmopathy of Graves disease can cause severe eye problems, including tethering of the extraocular muscles resulting in diplopia; involvement of the optic nerve, with some visual loss; and corneal ulceration because the lids do not close over the protruding eyeball (due to the exophthalmos).[22] The ophthalmopathy usually tends to stabilize after treatment of the hyperthyroidism. However, ophthalmopathy can worsen acutely after radioiodine treatment. Some physicians prescribe glucocorticoids for several weeks surrounding the radioiodine treatment if the person had signs of ophthalmopathy.[22] Ophthalmopathy can also be aggravated by smoking, which should be strongly discouraged. Figure 49.8 shows a woman with Graves disease.

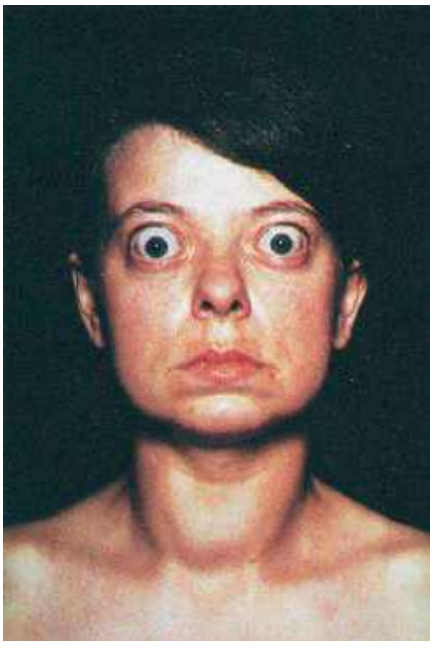


FIGURE 49.8 • Graves disease. A young woman with hyperthyroidism presented with a mass in the neck and exophthalmos. (From Rubin E., Strayer D. (Eds.), *Rubin's pathology: Clinicopathologic foundations of medicine* (6th ed., p. 1050, Figure 21.13). Philadelphia, PA: Lippincott Williams & Wilkins.)

Thyroid Storm

Thyroid storm, or thyrotoxic crisis, is an extreme and life-threatening form of thyrotoxicosis rarely seen today because of improved diagnosis and treatment methods.[24] When it does occur, it is seen most often in undiagnosed cases or in people with hyperthyroidism who have not been adequately treated. It is often precipitated by stress, such as an infection, by physical or emotional trauma, or by manipulation of a hyperactive thyroid gland during thyroidectomy.[24] Thyroid storm is manifested by a very high fever, extreme cardiovascular effects (*i.e.,* tachycardia, congestive failure, and angina), and severe CNS effects (*i.e.,* agitation, restlessness, and delirium).[24] The mortality rate is high.

Thyroid storm requires rapid diagnosis and implementation of treatment. Initially the person must be hemodynamically stabilized. The thyroid hormones can be removed by plasma pheresis, dialysis, or hemoperfusion adsorption.[24] Peripheral cooling is initiated with cold packs and a cooling mattress. For cooling to be effective, the shivering response must be prevented. General supportive measures to replace fluids, glucose, and electrolytes are essential during the hypermetabolic state. A β-adrenergic blocking drug, such as propranolol, is given to block the undesirable effects of T_4 on cardiovascular function. Glucocorticoids are used to correct the relative adrenal insufficiency resulting from the stress imposed by the hyperthyroid state and to inhibit the peripheral conversion of T_4 to T_3. Propylthiouracil or methimazole may be given to block thyroid synthesis.[24] Aspirin increases the level of free thyroid hormones by displacing the hormones from their protein carriers, and should not be used during thyroid storm.

IN SUMMARY

Thyroid hormones play a role in the metabolic process of almost all body cells and are necessary for normal physical and mental growth in the infant and young child. Alterations in thyroid function can manifest as a hypothyroid or a hyperthyroid state. Hypothyroidism can occur as a congenital or an acquired defect. Congenital hypothyroidism leads to mental retardation and impaired physical growth unless treatment is initiated during the first months of life. Acquired hypothyroidism leads to a decrease in metabolic rate and an accumulation of a mucopolysaccharide substance in the intercellular spaces; this substance attracts water and causes a mucous type of edema called *myxedema*. Hyperthyroidism causes an increase in metabolic rate and alterations in body function similar to those produced by enhanced sympathetic nervous system activity. Graves disease is characterized by the triad of hyperthyroidism, goiter, and ophthalmopathy.

DISORDERS OF ADRENAL CORTICAL FUNCTION

After completing this section of the chapter, you should be able to meet the following objectives:

- Describe the function of the adrenal cortical hormones and their feedback regulation.
- Relate the functions of the adrenal cortical hormones to Addison disease (*i.e.,* adrenal insufficiency) and Cushing syndrome (*i.e.,* glucocorticoid excess).

Control of Adrenal Cortical Function

The adrenal glands are small, bilateral structures that weigh approximately 5 g each and lie retroperitoneally at the apex of each kidney (Fig. 49.9). The medulla or inner portion of the gland (which constitutes approximately 20% of each adrenal) secretes epinephrine and norepinephrine and is part of the sympathetic nervous system.[4] The cortex

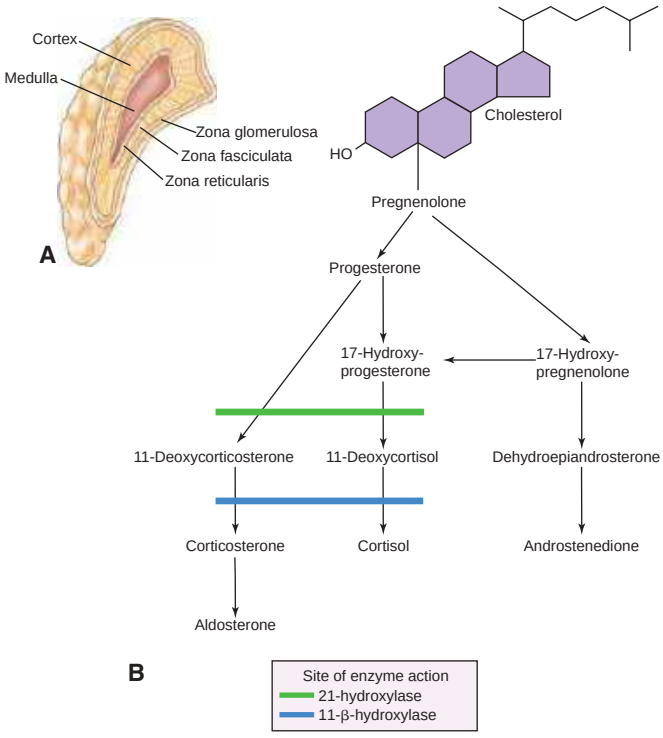


FIGURE 49.9 • (**A**) The adrenal gland, showing the medulla and the three layers of the cortex. The outer layer of the cortex (zona glomerulosa) is primarily responsible for mineralocorticoid production, and the middle layer (zona fasciculata) and the inner layer (zona reticularis) produce the glucocorticoids and the adrenal androgens. (**B**) Predominant biosynthetic pathways of the adrenal cortex. Critical enzymes in the biosynthetic process include 11-β-hydroxylase and 21-hydroxylase. A deficiency in one of these enzymes blocks the synthesis of hormones dependent on that enzyme and routes the precursors into alternative pathways.

forms the bulk of the adrenal gland (approximately 80%) and is responsible for secreting three types of hormones—the glucocorticoids, the mineralocorticoids, and the adrenal androgens.[4] Because the sympathetic nervous system also secretes epinephrine and norepinephrine, adrenal medullary function is not essential for life, but adrenal cortical function is. The total loss of adrenal cortical function is fatal in a few days to a few weeks if untreated.[4] This section of the chapter describes the synthesis and function of the adrenal cortical hormones and the effects of adrenal cortical insufficiency and excess.

Biosynthesis, Transport, and Metabolism

More than 30 hormones are produced by the adrenal cortex. Of these hormones, aldosterone is the principal mineralocorticoid, cortisol (hydrocortisone) is the major glucocorticoid, and androgens are the chief sex hormones. All of the adrenal cortical hormones have a similar structure in that all are steroids and are synthesized from acetate and cholesterol. Each of the steps involved in the synthesis of the various hormones requires a specific enzyme (see Fig. 49.9). The ACTH secreted by the anterior pituitary gland controls the secretion of the glucocorticoids and the adrenal androgens.

Cortisol, aldosterone, and the adrenal androgens are secreted in an unbound state and bind to plasma proteins for transport in the circulatory system. Cortisol binds largely to corticosteroid-binding globulin and to a lesser extent to albumin. Aldosterone and androgens circulate mostly bound to albumin. It has been suggested that the pool of protein-bound hormones may extend the duration of their action by delaying metabolic clearance.[4]

The main site for metabolism of the adrenal cortical hormones is the liver, where they undergo a number of metabolic conversions before being conjugated and made water-soluble. They are then eliminated in either the urine or the bile.

KEY POINTS

ADRENAL CORTICAL HORMONES

- The manifestations of primary adrenal cortical insufficiency are related mainly to mineralocorticoid deficiency (impaired ability to regulate salt and water elimination) and glucocorticoid deficiency (impaired ability to regulate blood glucose and control the effects of the immune and inflammatory responses).
- Adrenal cortical excess results in derangements in glucose metabolism, disorders of sodium and potassium regulation (increased sodium retention and potassium loss), impaired ability to respond to stress because of inhibition of inflammatory and immune responses, and signs of increased androgen levels such as hirsutism.

Adrenal Androgens

The adrenal androgens are synthesized primarily by the zona reticularis and the zona fasciculata of the cortex (see Fig. 49.9A).[4] These sex hormones probably exert little effect on normal sexual function. There is evidence, however, that the adrenal androgens (the most important of which is dehydroepiandrosterone [DHEA] and its sulfate [DHEAS]) contribute to the pubertal growth of body hair, particularly pubic and axillary hair in women. They may also play a role in steroid hormone economy of the pregnant woman and the fetal–placental unit. DHEAS is increasingly being used for treating both Addison disease and adults who have decreased levels of DHEAS. Adrenal androgens are physiologically important in women with Addison disease, and replacement with 25 to 50 mg of DHEAS daily should be considered.[18] Because the testes produce these hormones, there is no rationale for using it in men. The levels of DHEAS decline to approximately 10% to 20% of the levels of a 20-year-old by 80 years of age (*adrenopause*).[25] The value of routine replacement of DHEAS in the adrenopause is largely unproven.[25] DHEAS levels may represent another aging marker since it is involved with cardiovascular, immunological, and endocrine systems and may be a trend indicator for prevention of specific problems with aging.

Mineralocorticoids

The mineralocorticoids play an essential role in regulating potassium and sodium levels and water balance. They are produced in the zona glomerulosa, the outer layer of cells of the adrenal cortex. Aldosterone secretion is regulated by the renin–angiotensin mechanism and by blood levels of potassium. Increased levels of aldosterone promote sodium retention by the distal tubules of the kidney while increasing urinary losses of potassium.

Aldosterone is significant for balancing sodium, chloride, and potassium as well as maintaining the total body volume. To understand the importance of aldosterone consider that aldosterone controls approximately 90% of the mineralocorticoid function of the adrenals but cortisol also provides for mineralocorticoid function. Although aldosterone is responsible for about 3000 times greater the amount of mineralocorticoid activity than cortisol, there is nearly 2000 times more serum cortisol than aldosterone.[4] Due to the potency of aldosterone it is crucial that the body does not have excess or deficiency of this potent steroid. The consequences of excess aldosterone are low potassium and muscle weakness, while low amounts of aldosterone cause high potassium and cardiac toxicity.[4]

Glucocorticoids

The glucocorticoid hormones, mainly cortisol, are synthesized in the zona fasciculata and the zona reticularis of the adrenal gland.[4] The blood levels of these hormones are regulated by negative feedback mechanisms of the hypothalamic–pituitary–adrenal (HPA) system (Fig. 49.10). Just as other pituitary hormones are controlled by releasing factors from the hypothalamus, corticotropin-releasing hormone (CRH) is important in controlling the release of ACTH. Cortisol levels increase as

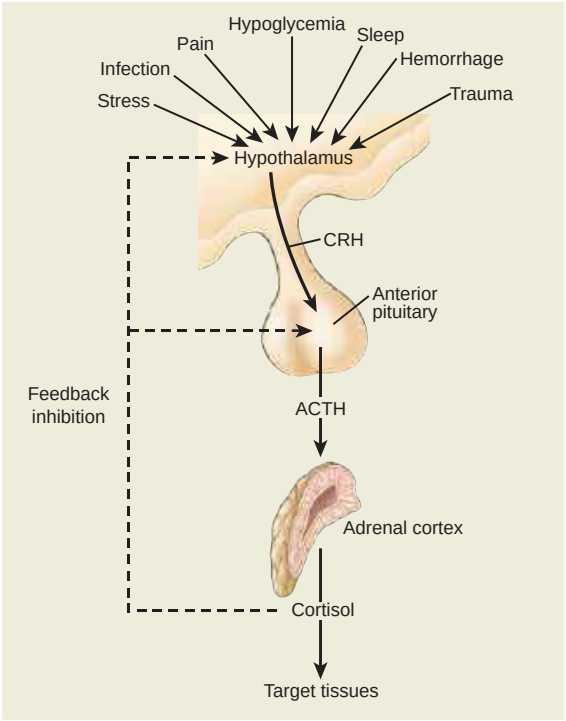


FIGURE 49.10 • The hypothalamic–pituitary-adrenal (HPA) feedback system that regulates glucocorticoid (cortisol) levels. Cortisol release is regulated by adrenocorticotropic hormone (ACTH). Stress exerts its effects on cortisol release through the HPA system and corticotropin-releasing hormone (CRH), which controls the release of ACTH from the anterior pituitary gland. Increased cortisol levels incite a negative feedback inhibition of ACTH release.

ACTH levels rise and decrease as ACTH levels fall. There is considerable diurnal variation in ACTH levels, which reach their peak in the early morning (around 6 to 8 AM) and decline as the day progresses. This appears to be due to rhythmic activity in the CNS, which causes bursts of CRH secretion and, in turn, ACTH secretion. This diurnal pattern is reversed in people who work during the night and sleep during the day. The rhythm may also be changed by physical and psychological stresses, endogenous depression, manic-depressive psychosis, and liver disease or other conditions that affect cortisol metabolism.[22]

The glucocorticoids perform a necessary function in response to stress and are essential for survival. When produced as part of the stress response, these hormones aid in regulating the metabolic functions of the body and in controlling the inflammatory response. The actions of cortisol are summarized in Table 49.4. Many of the anti-inflammatory actions attributed to cortisol result from the administration of pharmacologic levels of the hormone.

Metabolic Effects. Cortisol stimulates glucose production by the liver, promotes protein breakdown, and causes mobilization of fatty acids. As body proteins are broken down, amino acids are mobilized and transported to the liver, where they are used in the production of glucose (*i.e.,* gluconeogenesis). Mobilization of fatty acids converts cell metabolism from the use of glucose for energy to the use of fatty acids instead. As glucose production by the liver rises and peripheral glucose use falls, a moderate resistance to insulin develops. In people with diabetes and those who are diabetes prone, this has the effect of raising the blood glucose level.[22]

TABLE 49.4 ACTIONS OF CORTISOL

MAJOR INFLUENCE	EFFECT ON BODY
Glucose metabolism	Stimulates gluconeogenesis
	Decreases glucose use by the tissues
Protein metabolism	Increases breakdown of proteins
	Increases plasma protein levels
Fat metabolism	Increases mobilization of fatty acids
	Increases use of fatty acids
Anti-inflammatory action (pharmacologic levels)	Stabilizes lysosomal membranes of the inflammatory cells, preventing the release of inflammatory mediators
	Decreases capillary permeability to prevent inflammatory edema
	Depresses phagocytosis by white blood cells to reduce the release of inflammatory mediators
	Suppresses the immune response
	Causes atrophy of lymphoid tissue
	Decreases eosinophils
	Decreases antibody formation
	Decreases the development of cell-mediated immunity
	Reduces fever
	Inhibits fibroblast activity
Psychic effect	May contribute to emotional instability
Permissive effect	Facilitates the response of the tissues to humoral and neural influences, such as that of the catecholamines, during trauma and extreme stress

Psychological Effects. The glucocorticoid hormones appear to be involved directly or indirectly in emotional behavior. Receptors for these hormones have been identified in brain tissue, which suggests that they play a role in the regulation of behavior. People treated with adrenal cortical hormones have been known to display behavior ranging from mildly aberrant to psychotic.[22]

Immunologic and Inflammatory Effects. Cortisol influences multiple aspects of immunologic function and inflammatory responsiveness. Large quantities of cortisol are required for an effective anti-inflammatory action. This is achieved by the administration of pharmacologic rather than physiologic doses of synthetic cortisol. The increased cortisol blocks inflammation at an early stage by decreasing capillary permeability and stabilizing the lysosomal membranes so that inflammatory mediators are not released. Cortisol suppresses the immune response by reducing humoral and cell-mediated immunity. With this lessened inflammatory response comes a reduction in fever. During the healing phase, cortisol suppresses fibroblast activity and thereby lessens scar formation. Cortisol also inhibits prostaglandin synthesis, which may account in large part for its anti-inflammatory actions.

Pharmacologic Suppression of Adrenal Function

A highly significant aspect of long-term therapy with pharmacologic preparations of the glucocorticoids is adrenal insufficiency on withdrawal of drugs. The deficiency results from suppression of the HPA system. Chronic suppression causes atrophy of the adrenal gland, and the abrupt withdrawal of drugs can cause acute adrenal insufficiency. Recovery to a state of normal adrenal function may be prolonged, requiring up to 12 months or more.[22]

Tests of Adrenal Function

Several diagnostic tests can be used to evaluate adrenal cortical function and the HPA system.[11,22] Blood levels of cortisol, aldosterone, and ACTH can be measured using immunoassay methods. A 24-hour urine specimen measuring the excretion of various metabolic end products of adrenal hormones provides information about alterations in the biosynthesis of the adrenal cortical hormones. The 24-hour urinary free cortisol, late-night (between 11 PM and midnight) serum or salivary cortisol levels, and the overnight 1-mg dexamethasone suppression test are excellent screening tests for Cushing syndrome.[11,22]

Suppression and stimulation tests afford a means of assessing the state of the HPA feedback system. For example, a test dose of ACTH can be given to assess the response of the adrenal cortex to stimulation. Similarly, administration of dexamethasone, a synthetic glucocorticoid drug, provides a means of measuring negative feedback suppression of ACTH. Adrenal tumors and ectopic ACTH-producing tumors are usually unresponsive to ACTH suppression by dexamethasone. CRH tests can be used to diagnose a pituitary ACTH-secreting tumor (*i.e.,* Cushing disease).[22] Corticotropin (cosyntropin) stimulation testing is the most frequently used diagnostic test to assess testing responsiveness of the HPA axis.[22]

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH), or the adrenogenital syndrome, describes a congenital disorder caused by an autosomal recessive trait in which a deficiency exists in any of the enzymes necessary for the synthesis of cortisol[22] (see Fig. 49.10). A common characteristic of all types of CAH is a defect in the synthesis of cortisol that results in increased levels of ACTH and adrenal hyperplasia.[23] The increased levels of ACTH overstimulate the pathways for production of adrenal androgens. Mineralocorticoids may be produced in excessive or insufficient amounts, depending on the precise enzyme deficiency. Infants of both sexes are affected. Boys are seldom diagnosed at birth unless they have enlarged genitalia or lose salt and manifest adrenal crisis.[23] In female infants, an increase in androgens is responsible for creating the virilization syndrome of ambiguous genitalia with an enlarged clitoris, fused labia, and urogenital sinus (Fig. 49.11). In male and female children, other secondary sex characteristics are normal, and fertility is unaffected if appropriate therapy is instituted.

A spectrum of 21-hydroxylase deficiency states exists, ranging from simple virilizing CAH to a complete salt-losing enzyme deficiency. Simple virilizing CAH impairs the synthesis of cortisol, and steroid synthesis is shunted to androgen production. Persons with these deficiencies usually produce sufficient aldosterone or aldosterone intermediates to prevent signs and symptoms of mineralocorticoid deficiency. The salt-losing form is accompanied by deficient production of aldosterone and its intermediates. This results in fluid and electrolyte disorders after the fifth day of life (including hyponatremia, vomiting, dehydration, and shock). Hyperkalemia is not always present so it should not be considered a major screening diagnostic parameter.[25]

The 11-β-hydroxylase deficiency is rare and manifests a spectrum of severity. Affected people have excessive androgen production and impaired conversion of 11-deoxycorticosterone to corticosterone. The overproduction of 11-deoxycorticosterone, which has mineralocorticoid activity, is responsible for the hypertension that accompanies this deficiency. Diagnosis of CAH depends on the precise biochemical evaluation of metabolites in the cortisol pathway and on clinical signs and symptoms. Genetic testing is also invaluable. However, correlation between the phenotype and genotype is not always straightforward.[19,22]

Medical treatment of CAH includes oral or parenteral glucocorticoid replacement. Fludrocortisone acetate, a mineralocorticoid, may also be given to children who are salt losers.[22] Depending on the degree of virilization, reconstructive surgery during the first 2 years of life is indicated to reduce the size of the clitoris, separate the labia, and exteriorize the vagina.

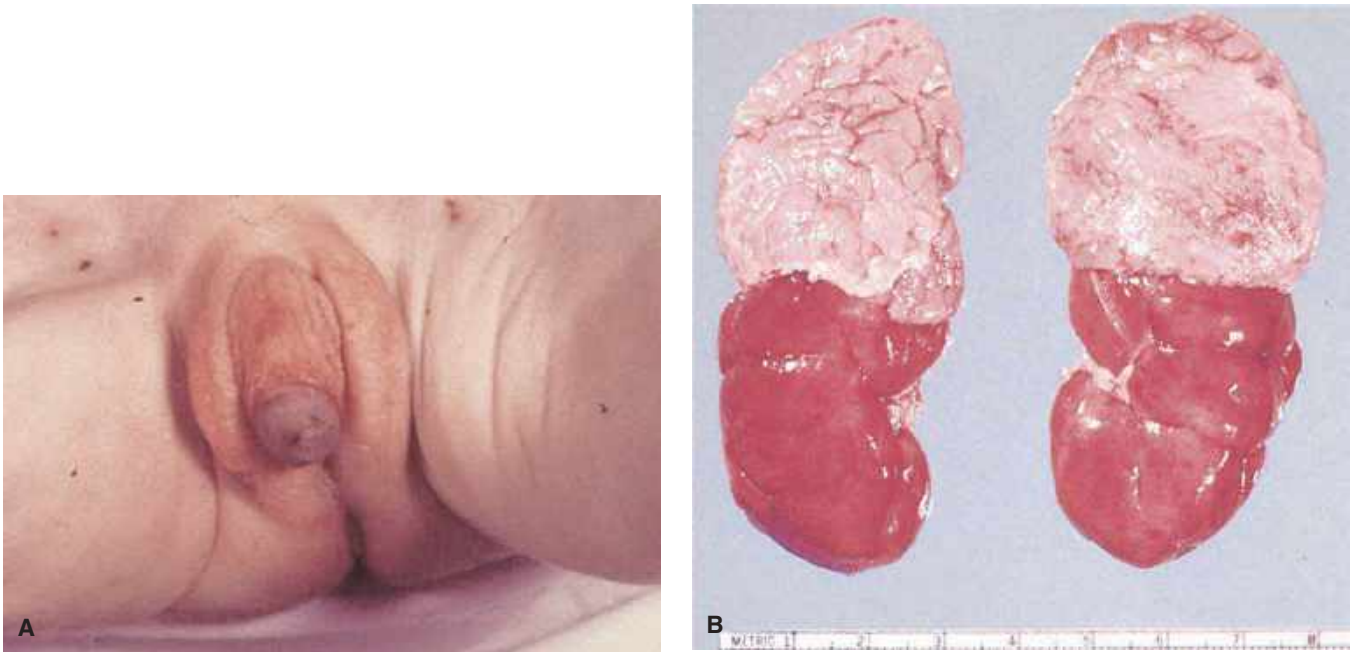


FIGURE 49.11 • Congenital adrenal hyperplasia (CAH). (**A**) A female infant with CAH demonstrating virilization of the genitalia with hypertrophy of the clitoris and partial fusion of labioscrotal folds. (**B**) A 7-week-old male died of severe salt-wasting CAH. At autopsy, both adrenal glands were markedly enlarged. (From Rubin E., Strayer D. (Eds.)., (2012). *Rubin's pathology: Clinicopathologic foundations of medicine* (6th ed., p. 1067, Figure 21.31). Philadelphia, PA: Lippincott Williams & Wilkins.)

Adrenal Cortical Insufficiency

There are two forms of adrenal insufficiency—primary and secondary[23] (see Table 49.5 for distinguishing features). Primary adrenal insufficiency, or Addison disease, is caused by destruction of the adrenal gland. Secondary adrenal insufficiency results from a disorder of the HPA system.

Primary Adrenal Cortical Insufficiency

Addison disease is reserved for primary adrenal insufficiency in which adrenal cortical hormones are deficient and ACTH levels are elevated because of lack of feedback inhibition.

Etiology and Pathogenesis. This disease is a relatively rare disorder in which all the layers of the adrenal cortex are destroyed. Autoimmune destruction is the most common cause of Addison disease in the United States. Before 1950, tuberculosis was the major cause of Addison disease in the United States and Canada, and it continues to be a major cause of the disease in countries where it is more prevalent. Rare causes include metastatic carcinoma, fungal infection (particularly histoplasmosis), cytomegalovirus infection, amyloid disease, and hemochromatosis. Bilateral adrenal hemorrhage may occur in persons taking anticoagulants, during open heart surgery, and during birth or major trauma. Adrenal insufficiency

TABLE 49.5 CLINICAL FINDINGS OF ADRENAL INSUFFICIENCY

FINDING	PRIMARY	SECONDARY/TERTIARY
Anorexia and weight loss	Yes (100%)	Yes (100%)
Fatigue and weakness	Yes (100%)	Yes (100%)
Gastrointestinal symptoms, nausea, diarrhea	Yes (50%)	Yes (50%)
Myalgia, arthralgia, abdominal pain	Yes (10%)	Yes (10%)
Orthostatic hypotension	Yes	Yes
Hyponatremia	Yes (85%–90%)	Yes (60%)
Hyperkalemia	Yes (60%–65%)	No
Hyperpigmentation	Yes (>90%)	No
Secondary deficiencies of testosterone, growth hormone, thyroxine, antidiuretic hormone	No	Yes
Associated autoimmune conditions	Yes	No

can be caused by acquired immunodeficiency syndrome, in which the adrenal gland is destroyed by a variety of opportunistic infectious agents. Drugs that inhibit synthesis or cause excessive breakdown of glucocorticoids can also result in adrenal insufficiency (*e.g.,* ketoconazole).

Clinical Manifestations. The adrenal cortex has a large reserve capacity, and the manifestations of adrenal insufficiency usually do not become apparent until approximately 90% of the gland has been destroyed.[4] These manifestations are related primarily to mineralocorticoid deficiency, glucocorticoid deficiency, and hyperpigmentation resulting from elevated ACTH levels. Although lack of the adrenal androgens (*i.e.,* DHEAS) exerts few effects in men because the testes produce these hormones, women have sparse axillary and pubic hair.

Mineralocorticoid deficiency causes increased urinary losses of sodium, chloride, and water, along with decreased excretion of potassium (Fig. 49.12). The result is hyponatremia, loss of extracellular fluid, decreased cardiac output, and hyperkalemia. There may be an abnormal appetite for salt. Orthostatic hypotension is common. Dehydration, weakness, and fatigue are common early symptoms. If loss of sodium and water is extreme, cardiovascular collapse and shock ensue. Because of a lack of glucocorticoids, the person with Addison disease has poor tolerance to stress. This deficiency causes hypoglycemia, lethargy, weakness, fever, and gastrointestinal symptoms such as anorexia, nausea, vomiting, and weight loss.

Hyperpigmentation results from elevated levels of ACTH. The skin looks bronzed or suntanned in exposed and unexposed areas, and the normal creases and pressure points tend to become especially dark. The gums and oral mucous membranes may become bluish-black. The amino acid sequence of ACTH is strikingly similar to that of melanocyte-stimulating hormone; hyperpigmentation occurs in greater than 90% of persons with Addison disease and is helpful in distinguishing the primary and secondary forms of adrenal insufficiency.[22]

Treatment. Addison disease, like type 1 diabetes mellitus, is a chronic metabolic disorder that requires lifetime hormone replacement therapy. The daily regulation of the chronic phase of Addison disease is usually accomplished with oral replacement therapy, with higher doses being given during periods of stress. The pharmacologic agent that is used should have both glucocorticoid and mineralocorticoid activity. Mineralocorticoids are needed only in primary adrenal insufficiency. Hydrocortisone is usually the drug of choice. In mild cases, hydrocortisone alone may be adequate. Fludrocortisone (a mineralocorticoid) is used for persons who do not obtain a sufficient salt-retaining effect from hydrocortisone. DHEAS replacement may also be helpful in the female patient.[22]

Because people with the disorder are likely to have episodes of hyponatremia and hypoglycemia, they need to have a regular schedule for meals and exercise. People with Addison disease also have limited ability to respond to infections, trauma, and other stresses. Such situations require immediate medical attention and treatment. People with Addison disease should be advised to wear a medical alert bracelet or medal.

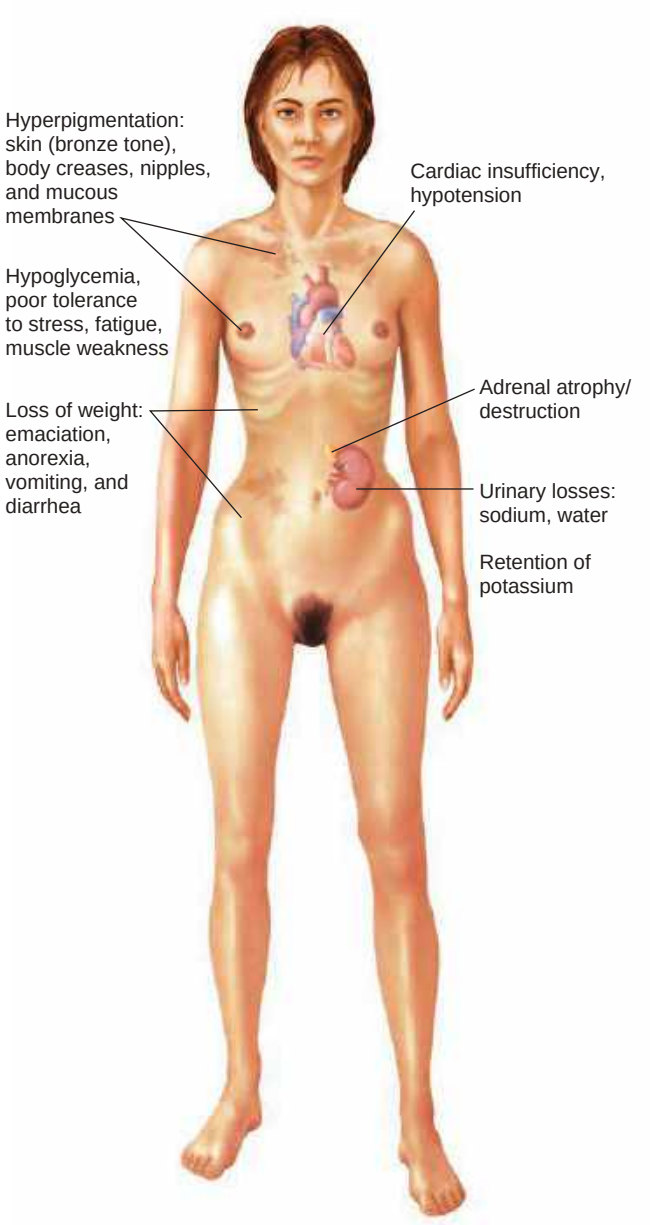


FIGURE 49.12 • Clinical manifestations of primary (Addison disease) and secondary adrenal insufficiency.

Secondary Adrenal Cortical Insufficiency

Secondary adrenal insufficiency can occur as the result of hypopituitarism or because the pituitary gland has been surgically removed. Tertiary adrenal insufficiency results from a hypothalamic defect. However, a far more common cause than either of these is the rapid withdrawal of glucocorticoids that have been administered therapeutically for asthma or an exacerbation of multiple sclerosis. These drugs suppress the HPA system, with resulting adrenal cortical atrophy and loss of cortisol production. This suppression continues long after drug therapy has been discontinued and can be critical during periods of stress or when surgery is performed.

Acute Adrenal Crisis

Acute adrenal crisis is a life-threatening situation.[23] If Addison disease is the underlying problem, exposure to even a minor illness or stress can precipitate nausea, vomiting, muscular weakness, hypotension, dehydration, and vascular collapse. The onset of adrenal crisis may be sudden, or it may progress over a period of several days. The symptoms may occur suddenly in children with salt-losing forms of CAH.[23] Massive bilateral adrenal hemorrhage causes an acute fulminating form of adrenal insufficiency. Hemorrhage can be caused by meningococcal septicemia, adrenal trauma, anticoagulant therapy, adrenal vein thrombosis, or adrenal metastases.

Adrenal insufficiency is treated with hormone replacement therapy that includes a combination of glucocorticoids and mineralocorticoids. For acute adrenal insufficiency, the *five Ss* of management should be followed: (1) *S*alt replacement, (2) *S*ugar (dextrose) replacement, (3) *S*teroid replacement, (4) *S*upport of physiologic functioning, and (5) *S*earch for and treat the underlying cause (*e.g.,* infection). Extracellular fluid volume should be restored with several liters of 0.9% saline and 5% dextrose. Glucocorticoid replacement is accomplished through the intravenous administration of either dexamethasone or hydrocortisone. Dexamethasone is preferred acutely for two reasons: it is long acting (12 to 24 hours) and it does not interfere with measurement of serum or urinary steroids during subsequent corticotropin (ACTH) stimulation tests if diagnosis needs to be established. Thereafter, hydrocortisone is given either intravenously or intramuscularly at 6-hour intervals and then tapered over 1 to 3 days to maintenance levels. Oral hydrocortisone replacement therapy can be resumed once the saline infusion has been discontinued and the person is taking food and fluids by mouth. Mineralocorticoid therapy is not required when large amounts of hydrocortisone are being given, but as the dose is reduced it is usually necessary to add fludrocortisone. Glucocorticoid and mineralocorticoid replacement therapy is monitored using heart rate and blood pressure measurements; serum electrolyte values; and titration of plasma renin activity into the upper-normal range.[22]

Glucocorticoid Hormone Excess (Cushing Syndrome)

The term *Cushing syndrome* refers to the manifestations of hypercortisolism from any cause.[23] Three important forms of Cushing syndrome result from excess glucocorticoid production by the body. One is a pituitary form, which results from excessive production of ACTH by a tumor of the pituitary gland. This form of the disease was the one originally described by Cushing. Therefore, it is called *Cushing disease*. The second form is the adrenal form, caused by a benign or malignant adrenal tumor. The third form is ectopic Cushing syndrome, caused by a nonpituitary ACTH-secreting tumor. Certain extrapituitary malignant tumors such as small cell carcinoma of the lung may secrete ACTH or, rarely, CRH, and produce Cushing syndrome. Cushing syndrome can also result from long-term therapy with one of the potent pharmacologic preparations of glucocorticoids; this form is called *iatrogenic Cushing syndrome*.

Clinical Manifestations

The major manifestations of Cushing syndrome represent an exaggeration of the many actions of cortisol (see Table 49.4). Altered fat metabolism causes a peculiar deposition of fat characterized by a protruding abdomen; subclavicular fat pads or "buffalo hump" on the back; and a round, plethoric "moon face" (Figs. 49.13 and 49.14). There is muscle weakness, and the extremities are thin because of protein breakdown and muscle wasting. In advanced cases, the skin over the forearms and legs becomes thin, having the appearance of parchment. Purple striae, or stretch marks, from stretching of the catabolically weakened skin and subcutaneous tissues are distributed

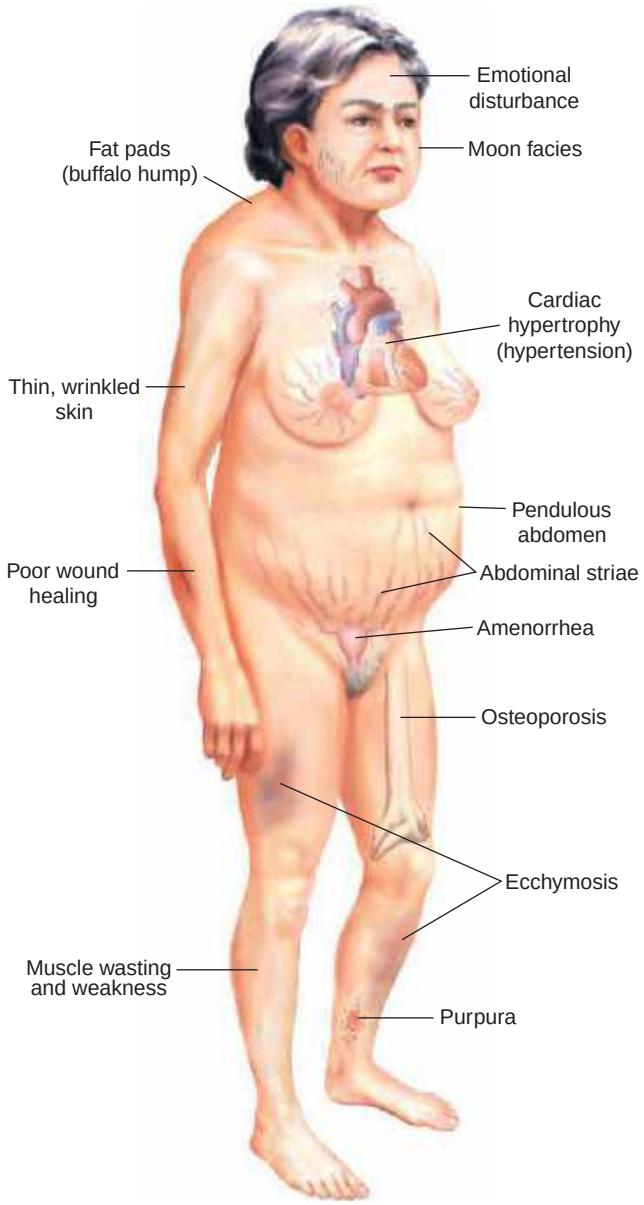


FIGURE 49.13 • Clinical features of Cushing syndrome.

FIGURE 49.14 • Cushing syndrome. A woman who suffered from a pituitary adenoma that produced ACTH exhibits a moon face, buffalo hump, increased facial hair, and thinning of the scalp hair. (Rubin E., Strayer D. (Eds.), (2012). *Rubin's pathology: Clinicopathologic foundations of medicine* (6th ed., p. 1073, Figure 21.37). Philadelphia, PA: Lippincott Williams & Wilkins.)

over the breast, thighs, and abdomen. Osteoporosis may develop because of destruction of bone proteins and alterations in calcium metabolism, resulting in back pain, compression fractures of the vertebrae, and rib fractures. As calcium is mobilized from bone, renal calculi may develop.[22]

The glucocorticoids possess mineralocorticoid properties. This causes hypokalemia, as a result of excessive potassium excretion, and hypertension, resulting from sodium retention. Inflammatory and immune responses are inhibited, resulting in increased susceptibility to infection. Cortisol increases gastric acid secretion, which may provoke gastric ulceration and bleeding. An accompanying increase in androgen levels causes hirsutism, mild acne, and menstrual irregularities in women. Excess levels of the glucocorticoids may give rise to extreme emotional lability, ranging from mild euphoria and absence of normal fatigue to grossly psychotic behavior.

Diagnosis and Treatment

Diagnosis of Cushing syndrome depends on the finding of cortisol hypersecretion. The determination of 24-hour excretion of cortisol in urine provides a reliable and practical index of cortisol secretions. One of the prominent features of Cushing syndrome is loss of the diurnal pattern of cortisol secretion. The overnight 1-mg dexamethasone suppression test is also used as a screening tool for Cushing syndrome.

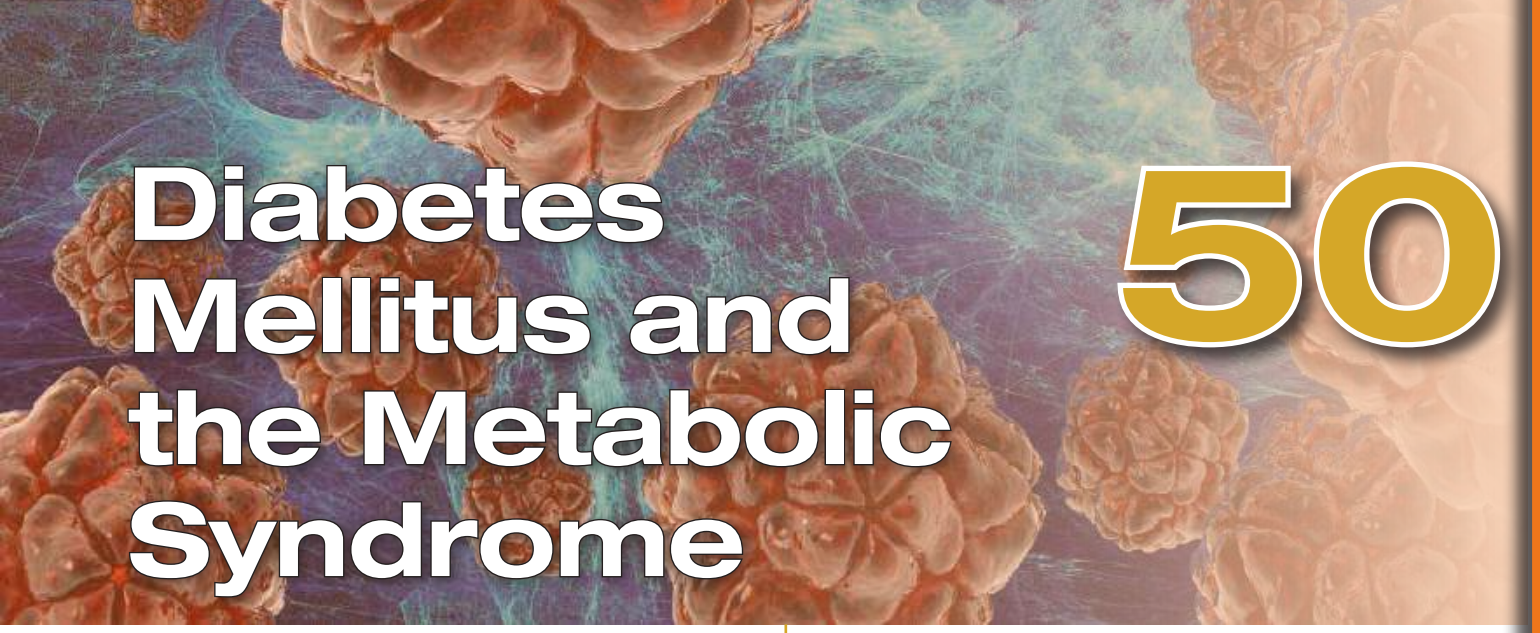
Other tests include measurement of the plasma levels of ACTH.[22] ACTH levels should be normal or elevated in ACTH-dependent Cushing syndrome (Cushing disease and ectopic ACTH), and low in non–ACTH-dependent Cushing syndrome (adrenal tumors). Various suppression or stimulation tests of the HPA system are performed to delineate the cause further. MRI or CT scans afford a means for locating adrenal or pituitary tumors.

Untreated, Cushing syndrome produces serious morbidity and even death. The choice of surgery, irradiation, or pharmacologic treatment is determined largely by the cause of the hypercortisolism. The goal of treatment for Cushing syndrome is to remove or correct the source of hypercortisolism without causing permanent pituitary or adrenal damage. Transsphenoidal removal of a pituitary adenoma or a hemihypophysectomy is the preferred method of treatment for Cushing disease. This allows removal of only the tumor rather than the entire pituitary gland. After successful removal, the person must receive cortisol replacement therapy for 6 to 12 months or until adrenal function returns. People may also receive pituitary radiation therapy, but the full effects of treatment may not be realized for 3 to 12 months. Unilateral or bilateral adrenalectomy may be done in the case of adrenal adenoma. When possible, ectopic ACTH-producing tumors are also removed. Pharmacologic agents that block steroid synthesis (*i.e.,* mitotane, ketoconazole, and metyrapone) may be used to treat people with ectopic tumors or adrenal carcinomas that cannot be resected.[26] Many of these people also require *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*) pneumonia prophylaxis because of the profound immunosuppression caused by the excessive glucocorticoid levels.

Incidental Adrenal Mass

An incidentaloma is a mass lesion found unexpectedly in an adrenal gland by an imaging procedure (done for other reasons), most commonly CT (but also MRI and ultrasonography).[22] Incidentalomas can also occur in other organs (*e.g.,* pituitary, thyroid). The two most important points to establish regarding incidentalomas are if they are malignant and if they are hormonally active.

Primary adrenal carcinoma is quite rare, but other cancers, particularly lung cancers, commonly metastasize to the adrenal gland (other cancers include breast, stomach, pancreas, colon, kidney, melanomas, and lymphomas). The size and imaging characteristics of the mass may help determine whether the tumor is benign or malignant. Appropriate screening to exclude a hormonally active lesion includes tests to rule out pheochromocytoma, Cushing syndrome, and Conn syndrome (mineralocorticoid excess).



Diabetes Mellitus and the Metabolic Syndrome

50

Sally Gerard

According to the American Diabetes Association (ADA), diabetes mellitus (DM) is a chronic health problem affecting 25.8 million people in the United States (approximately 8.3% of the population).[1] It is so prevalent that the term "diabetes" is used interchangeably with diabetes mellitus, even though another form of diabetes exists (diabetes insipidus; see Chapter 39). One million of these people have type 1 diabetes; the remainder have type 2 diabetes. In addition, another 79 million people have been categorized with "prediabetes." Prediabetes and diabetes affect people in all age groups and from all walks of life. Diabetes is more prevalent among American Indians/Alaska Natives (16.8%), non-Hispanic African Americans (12.6%), and Hispanic Americans (11.85%).[1]

Diabetes, and the resulting impact of short-term and long-term blood glucose fluctuations, can lead to a variety of complications, ranging from acute medical emergencies to disability and death. Diabetes is a significant risk factor in coronary heart disease and stroke, and it is the leading cause of blindness and chronic kidney disease, as well as a common cause of lower extremity amputations.[2] Optimizing glycemic control, through a variety of interventions, minimizes the complications associated with diabetes.

DIABETES MELLITUS

After completing this section of the chapter, you should be able to meet the following objectives:

- Compare the distinguishing features of type 1 and type 2 DM and cite the criteria for gestational diabetes.
- Define the metabolic syndrome and describe its associations with the development of type 2 diabetes.
- Characterize the blood glucose–lowering actions of the hypoglycemic agents used in treatment of type 2 diabetes.
- Name and describe the types (according to duration of action) of insulin.

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the characteristic of hyperglycemia.[7] Prior to the discovery of insulin in the 1920s, diabetes

was a fatal disease. The incidence of type 2 diabetes has risen dramatically over the past century and will continue to rise in the United States with the increasing prevalence of obesity, aging of the population, decreasing mortality, and growth of minority populations. Diabetes is a disorder of carbohydrate, protein, and fat metabolism resulting from an imbalance between insulin availability and insulin need. Factors contributing to imbalance include reduced insulin secretion, decreased glucose utilization, and increased glucose production.[7] A person with uncontrolled diabetes is unable to transport glucose into fat and muscle cells. As a result, body cells are starved, and the breakdown of fat and protein is increased to generate alternative fuels.

Classification and Etiology

Although DM clearly is a disorder of insulin availability, it is not a single disease. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus developed a revised system for the classification of diabetes in 1997[7] (Chart 50.1). Two broad categories of DM are type 1 and type 2. Type 2 diabetes currently accounts for about 90% to 95% of the cases of diabetes. Other categories of DM are gestational diabetes mellitus (GDM) (*i.e.*, diabetes that develops during pregnancy) and other specific types of diabetes, many of which occur secondary to other conditions (*e.g.*, Cushing syndrome, acromegaly, pancreatitis).[7]

The revised classification system also includes a system for diagnosing diabetes according to stages of glucose intolerance[7] (Table 50.2). The revised criteria recognized a group of people whose glucose levels, although not meeting criteria for diabetes, are, nevertheless, too high to be considered normal.[8] This group of people, labeled together as people with *prediabetes*, *includes impaired glucose tolerance* (IGT) and *impaired fasting glucose* (IFG). A fasting plasma glucose (FPG) of less than 100 mg/dL (5.5 mmol/L) or a 2-hour oral glucose tolerance test (OGTT) result of less than 140 mg/dL is considered normal. IGT reflects abnormal plasma glucose measurements (140 to 199 mg/dL [7.8 to 11.0 mmol/L]) 2 hours after a 75-g oral glucose load.[8] IFG is defined by an elevated FPG concentration (100 to 125 mg/dL [5.6 to 6.9 mmol/L]). IGT and IFG (*i.e.*, prediabetes) categories are associated with increased risk of atherosclerotic heart disease and increased risk of progression to type 2 diabetes.[8] IGT and IFG have different rates of progression to diabetes because of different

CHART 50.1 ETIOLOGIC CLASSIFICATIONS OF DM

Type 1 diabetes (beta cell destruction, absolute insulin deficiency)
- A. Immune mediated
- B. Idiopathic

Type 2 diabetes (insulin resistance with relative insulin deficiency)

Other specific types
- – Genetic defects of beta cell function (*i.e.*, maturity onset diabetes of the young)
- – Genetic defects in insulin action (*i.e.*, type A insulin resistance)
- – Diseases of the exocrine pancreas
- – Endocrinopathies (*i.e.*, Cushing disease, acromegaly)
- – Drug or chemical induced (*i.e.*, glucocorticoids)
- – Infections (*i.e.*, cytomegalovirus, rubella)
- – Other genetic syndromes (*i.e.*, Turner syndrome, Down syndrome)

Gestational diabetes mellitus

Adapted from the American Diabetes Association (2011) and Rubin R., Strayer D. S. (2012). Rubin's pathology: Clinicopathologic foundations of medicine (6th ed., p. 1088). Philadelphia, PA: Lippincott Williams & Wilkins, Table 22.3.

TABLE 50.2 CLASSIFICATION OF DIABETES USING FASTING* PLASMA GLUCOSE AND OGTTS

TEST	NORMOGLYCEMIC	IFG†	IGT†	DM‡
FPG	<100 mg/dL (5.6 mmol/L)	100–125 mg/dL (5.6–6.9 mmol/L)		≥126 mg/dL (7.0 mmol/L)
2-hour OGTT§	<140 mg/dL (7.8 mmol/L)		140–199 mg/dL (7.8–11.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)
Other				Symptoms of DM and casual plasma glucose ≥200 mg/dL (11.1 mmol/L)

*Fasting is defined as no caloric intake for at least 8 hours.
†IFG and IGT are prediabetes states and can occur in isolation or together in a given subject.
‡In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a separate day.
§OGTT with 2-hour measurement of venous plasma or serum glucose after a 75-g carbohydrate load.
FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGGT, oral glucose tolerance test; DM, diabetes mellitus
Developed from data in American Diabetes Association. (2013). Standards of medical care in diabetes-2013. *Diabetes Care* 36(Suppl. 1), S11–S66.

CHART 50.2 CRITERIA FOR DIAGNOSIS OF DM

1. HbA_{1c}* ≥ 6.5%

OR

2. FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.

OR

3. 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during and OGTT.

OR

4. In a person with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose of ≥200 mg/dL (11.1 mmol/L)

In the absence of unequivocal hyperglycemia, criteria 1 to 2 should be confirmed by repeat testing.
FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_1c; OGTT, oral glucose tolerance test.
Adapted from the American Diabetes Association (2011) and Rubin R., Strayer D. S. (2012). *Rubin's pathology: Clinicopathologic foundations of medicine* (6th ed., p. 1089). Philadelphia, PA: Lippincott Williams & Wilkins, Table 22.4.

pathophysiologic mechanisms. The criteria in Chart 50.2 are used to confirm the diagnosis of people with prediabetes. Interventions for people with prediabetes, such as calorie reduction, increased physical activity, and weight reduction, are beneficial to decrease the risk of disease development.[8]

Type 1 Diabetes Mellitus

Type 1 DM is characterized by destruction of the pancreatic beta cells.[8] Type 1 diabetes can be subdivided into two types—type 1A immune-mediated diabetes and type 1B idiopathic (non–immune-related) diabetes. In the United States and Europe, approximately 90% to 95% of people with type 1 DM have type 1A immune-mediated diabetes. The onset of type 1B is less common and does not seem to have an autoimmune component.[7] From a treatment perspective, the types of type 1 diabetes are not differentiated.

Type 1A Immune-Mediated Diabetes. Type 1A diabetes, commonly referred to simply as type 1 diabetes, is characterized by immune-mediated destruction of beta cells.[8] This type of diabetes, formerly called *juvenile diabetes*, occurs more commonly in young people but can occur at any age.[9] The rate of beta cell destruction is quite variable, being rapid in some people and slow in others. The rapidly progressive form is commonly observed in children, but also may occur in adults. The slowly progressive form usually occurs in adults and is sometimes referred to as *latent autoimmune diabetes in adults* (LADA).

Type 1 diabetes is a catabolic disorder characterized by an absolute lack of insulin, an elevation in blood glucose, and a breakdown of body fats and proteins.[9] The absolute lack of insulin in people with type 1 DM means that they are particularly prone to the development of ketoacidosis. One of the actions of insulin is the inhibition of *lipolysis* (*i.e.*, fat breakdown) and release of free fatty acids (FFA) from fat cells.[7] In the absence of insulin, ketosis develops when these fatty acids are released from fat cells and converted to ketones in the liver. Because of the loss of insulin response, *all people with type 1A diabetes require exogenous insulin replacement* to reverse the catabolic state, control blood glucose levels, and prevent ketosis.[9]

Type 1A diabetes is thought to be an autoimmune disorder resulting from a genetic predisposition (*i.e.*, diabetogenic genes); an environmental triggering event, such as an infection; and a T-lymphocyte–mediated hypersensitivity reaction against some beta cell antigen. Susceptibility to type 1A DM involves multiple genes. The major susceptibility gene for type 1A DM is located in the human leukocyte antigen (HLA) region on chromosome 6.[7] Much evidence has focused on the inherited major histocompatibility complex (MHC) genes on chromosome 6 that encode HLAs. Although the risk of developing type 1 diabetes is increased 10-fold in relatives of people with the disease, the overall risk is relatively low. Approximately 3% to 4% of children develop type 1 diabetes when a parent has the disease.[9] Diabetes autoantibodies have been used to predict risk for type 1 diabetes and to classify people with diabetes as having an immune-mediated beta cell destructive process.[10]

Type 1A diabetes–associated autoantibodies may exist for years before the onset of hyperglycemia. There are two major types of autoantibodies—insulin autoantibodies (IAAs), and islet cell autoantibodies and antibodies directed at other islet autoantigens, including glutamic acid decarboxylase (GAD) and the protein tyrosine phosphatase IA-2.[9] Testing for antibodies to GAD or IA-2 and for IAAs using sensitive radiobinding assays can identify more than 85% of cases of new or future type 1 diabetes.[10] The appearance of IAAs may precede that of antibodies to GAD or IA-2, and IAAs may be the only antibodies detected at diagnosis in young children.[10] These people also may have other autoimmune disorders such as Graves disease, rheumatoid arthritis, and Addison disease. Research continues to investigate the role of diabetes autoantibodies in the future of type 1 diabetes interventions.

The fact that type 1 diabetes is thought to result from an interaction between genetic and environmental factors has led to research into methods directed at prevention and early control of the disease.[11] These methods include the identification of genetically susceptible people and early intervention in newly diagnosed people with type 1 diabetes. After the diagnosis of type 1 diabetes, there is often a short period of beta cell regeneration, during which symptoms of diabetes disappear and insulin injections are reduced or not needed. This is sometimes called the *honeymoon period*. Immune interventions (immunomodulation) designed to interrupt the destruction of beta cells before development of type 1 diabetes are being investigated in various trials.[6] Unfortunately, none of the interventions studied to date has shown real clinical utility.[6]

In the unit opener case study we met Emily Toronto, the 7-year-old diagnosed with type 1 diabetes. Emily had classic symptoms of severe hyperglycemia, the associated dehydration (osmotic diuresis), and metabolic acidosis. Because she was at risk for diabetes, due to her family history, she may have had testing for the presence of diabetes autoantibodies. Regardless of whether Emily has type 1A or type 1B, the treatment of her acute or long-term management is the same. Treatment of her acute needs will be discussed in more detail in the section on diabetic ketoacidosis (DKA).

Type 2 Diabetes Mellitus and the Metabolic Syndrome

Type 2 DM accounts for the majority of cases of diabetes, approximately 90% to 95%.[1] It is a heterogeneous condition that describes the presence of hyperglycemia in association with *relative* insulin deficiency. Autoimmune destruction of the beta cells does not occur. Although many people with type 2 diabetes are adults and overweight, recent trends indicate type 2 diabetes has become a more common occurrence in obese adolescents and children.[7] Also, people with type 2 diabetes eventually may require insulin. Therefore, the previous terms related to type 2 diabetes, such as *adult onset diabetes* and *non–insulin-dependent diabetes*, can generate confusion and are thus obsolete.[7]

Type 2 diabetes has a strong genetic component. A number of genetic and acquired pathogenic factors have been implicated in the progressive impairment of beta cell function in persons with prediabetes and type 2 diabetes. People with one parent with type 2 diabetes have an increased risk for developing the disease. If both parents have the disease, the risk is approximately 40%.[9] Despite strong familial predisposition, the genetics of type 2 diabetes is poorly defined. Research in the field of type 2 diabetes has identified genetic alterations associated with altered insulin secretions, but these studies are ongoing.[9]

The metabolic abnormalities that lead to type 2 diabetes include:

1. Insulin resistance.
2. Deranged secretion of insulin by the pancreatic beta cells.
3. Increased glucose production by the liver[6,7] (Fig. 50.6).

In contrast to type 1 diabetes, where *absolute* insulin deficiency is present, people with type 2 diabetes can have high, normal, or low insulin levels. Insulin resistance is the decreased ability of insulin to act effectively on target tissues, especially muscle, liver, and fat. It is the predominate characteristic of type 2 diabetes and results from a combination of factors such as genetic susceptibility and obesity.[9] Table 50.3 compares the characteristics of type 1 and type 2 DM.

Insulin resistance initially stimulates an increase in insulin secretion, often to a level of modest hyperinsulinemia, as the beta cells attempt to maintain a normal blood glucose level. In time, the increased demand for insulin secretion leads to beta cell exhaustion and failure.[9] This results in elevated postprandial blood glucose levels and an eventual increase in glucose production by the liver. Because people with type 2 diabetes do not have an absolute insulin deficiency, they are less prone to ketoacidosis compared to people with type 1 diabetes.[12]

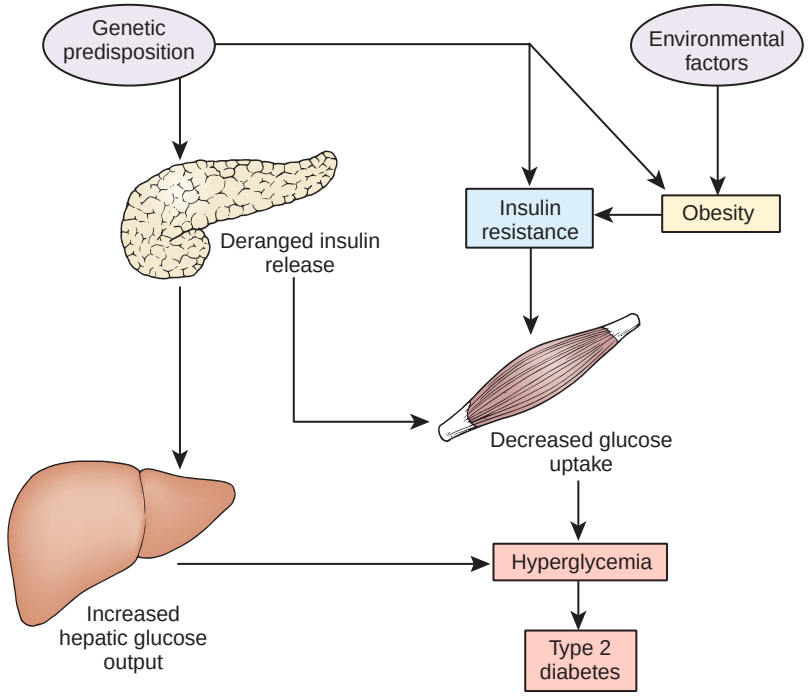


FIGURE 50.6 • Pathogenesis of type 2 DM.

TABLE 50.3 COMPARISON OF TYPE 1 AND TYPE 2 DM

	TYPE 1 DIABETES	TYPE 2 DIABETES
Age of onset	Usually before 20	Usually after 30
Type of onset	Abrupt; symptomatic (polyuria, polydipsia, dehydration) often with severe ketoacidosis	Gradual; usually subtle; often asymptomatic
Usual body weight	Normal; recent weight loss is common	Overweight
Family history	<20%	>60%
Monozygotic twins	50% concordant	90% concordant
HLA associations	+	No
Islet lesions	Early-inflammation Late—atrophy and fibrosis	Late-fibrosis, amyloid
Beta cell mass	Markedly reduced	Normal or slightly reduced
Circulating insulin level	Markedly reduced	Elevated or normal
Clinical management	Insulin absolutely required	Insulin usually not needed initially; insulin supplementation may be needed at later stages; weight loss typically improves the condition

HLA, human leukocyte antigen.

In the basal state, hepatic insulin resistance is manifested by overproduction of glucose despite fasting hyperinsulinemia, with the rate of glucose production being the primary determinant of the elevated FPG in people with type 2 diabetes.[9,12] Although the insulin resistance seen in people with type 2 diabetes can be caused by a number of factors, it is strongly associated with obesity and physical inactivity.[12]

Specific causes of beta cell dysfunction are unclear but seem to include an initial decrease in the beta cell mass related to genetic or prenatal factors (*e.g.*, intrauterine growth retardation); increased apoptosis or decreased beta cell regeneration; beta cell exhaustion due to long-standing insulin resistance; glucotoxicity (*i.e.*, glucose toxicity–induced beta cell desensitization); lipotoxicity (*i.e.*, toxic effects of lipids on beta cells); and amyloid deposition or other conditions that have the potential to reduce beta cell mass.[2,9]

Insulin Resistance and the Metabolic Syndrome. There is increasing evidence to suggest that insulin resistance not only contributes to the hyperglycemia in people with type 2 diabetes, but may play a role in other metabolic abnormalities.[13] These include obesity, high levels of plasma triglycerides and low levels of high-density lipoproteins (HDL), hypertension, systemic inflammation (as detected by C-reactive protein [CRP] and other mediators), abnormal fibrinolysis, abnormal function of the vascular endothelium, and macrovascular disease (coronary artery, cerebrovascular, and peripheral arterial disease).[13] This constellation of abnormalities is often referred to as the *insulin resistance syndrome*, *syndrome X*, or, the preferred term, *metabolic syndrome*.[13] The clinical signs, laboratory abnormalities, and associated illnesses associated with this syndrome are described in Chart 50.3. Insulin resistance and increased risk of developing type 2 diabetes are also seen in women with polycystic ovary syndrome.[9]

A major factor in people with metabolic syndrome that leads to type 2 diabetes is obesity.[8,13] Approximately 80% to 90% of people with type 2 diabetes are overweight.[1,12] Obese people have increased resistance to the action of insulin and impaired suppression of glucose production by the liver, resulting in both hyperglycemia and hyperinsulinemia.[14] The type of obesity is an important consideration in the development

CHART 50.3 FREQUENTLY OBSERVED CONCOMITANTS OF THE INSULIN RESISTANCE/METABOLIC SYNDROME

Clinical Signs
- Central (upper body) obesity with increased waist circumference
- Acanthosis nigricans (hypertrophic, hyper pigmented skin changes)

Laboratory Abnormalities
- Elevated fasting and/or postprandial glucose
- Insulin resistance with hyperinsulinemia
- Dyslipidemia characterized by increased triglycerides and low HDL cholesterol
- Abnormal thrombolysis
- Hyperuricemia
- Endothelial and vascular smooth muscle dysfunction
- Albuminuria

Comorbid Illnesses
- Hypertension
- Atherosclerosis
- Hyperandrogenism with polycystic ovary syndrome

From Rubin R., Strayer D. S. (2012). *Rubin's pathology: Clinicopathologic foundations of medicine* (6th ed., p. 1089). Philadelphia, PA: Lippincott Williams & Wilkins, Table 22.3.

of type 2 diabetes. It has been found that people with upper body (or central) obesity are at greater risk for developing type 2 diabetes and metabolic disturbances than people with lower body (or peripheral) obesity.[13] Waist circumference and waist–hip ratio (WHR), which are both surrogate measures of central obesity, have been shown to correlate well with insulin resistance.[12] For management, weight loss with an initial loss of 5% to 10% of body weight should be incorporated into the treatment plan, as well as addressing the diabetes and other related metabolic abnormalities.

It has been theorized that the insulin resistance and increased glucose production in obese people with type 2 diabetes may stem from an increased concentration of FFAs.[3,7] This has several consequences:

1. Excessive and chronic elevation of FFAs can cause beta cell dysfunction (lipotoxicity).
2. FFAs act at the level of the peripheral tissues to cause insulin resistance and glucose underutilization by inhibiting glucose uptake and glycogen storage.
3. The accumulation of FFAs and triglycerides reduces hepatic insulin sensitivity, leading to increased hepatic glucose production and hyperglycemia, especially in the fasting state.[14]

Thus, the increase in FFAs that occurs in obese people (especially visceral obesity) with a genetic predisposition to type 2 diabetes may eventually lead to beta cell dysfunction, increased insulin resistance, and greater hepatic glucose production. A further consequence is the diversion of excess FFAs to nonadipose tissues, including the liver, skeletal muscle, heart, and pancreatic beta cells.[3,14] In the liver, the uptake of FFAs from the portal blood can lead to hepatic triglyceride accumulation and nonalcoholic fatty liver disease.

KEY POINTS

DIABETES MELLITUS

- DM is a disorder of carbohydrate, fat, and protein metabolism brought about by impaired beta cell synthesis or release of insulin, or the inability of tissues to use insulin.
- Type 1 diabetes results from loss of beta cell function and an absolute insulin deficiency.
- Type 2 diabetes results from impaired ability of the tissues to use insulin (insulin resistance) accompanied by a relative lack of insulin or impaired release of insulin in relation to blood glucose levels (beta cell dysfunction).

Other Specific Types of Diabetes

A small percentage of the overall number of cases of diabetes consist of specific types of diabetes associated with certain other conditions and syndromes. Such diabetes can occur with pancreatic disease or the removal of pancreatic tissue and with endocrine diseases, such as acromegaly, Cushing syndrome, or pheochromocytoma.[8] Endocrine disorders that produce hyperglycemia do so by increasing the hepatic production of glucose or decreasing the cellular use of glucose.[3] Several specific types of diabetes are associated with monogenetic defects in beta cell function. Other causes for diabetes can be genetic defects in beta cell function or insulin secretion, drug treatment, or chemicals.[7]

Several medications commonly used for treatment of other diseases can cause significant alterations in glucose. For example, diuretics, specifically thiazide and loop diuretics, can elevate blood glucose.[15] These diuretics increase potassium loss, which is thought to impair beta cell release of insulin. Other drugs and therapies known to cause hyperglycemia include diazoxide, glucocorticoids, oral contraceptives, antipsychotic agents, and total parenteral nutrition (*i.e.*, hyperalimentation).[6] Drug-related increases in blood glucose usually are reversed after the drug has been discontinued although many of them are taken for chronic conditions and must be considered in the long-term treatment of glucose control.

Gestational Diabetes

GDM is any degree of glucose intolerance that occurs initially during pregnancy. GDM affects approximately 7% of pregnancies.[16] It occurs most commonly in African American, Hispanic/Latino American, and American Indian women. It most frequently affects:

- Women with a family history of diabetes.
- Women with a history of stillbirth or spontaneous abortion.
- Women who are obese.
- Women who are of advanced maternal age.
- Women who have had five or more pregnancies.[16]

Diagnosis. In light of the increasing incidence of obesity and onset of type 2 diabetes in younger populations, the ADA established revised guidelines for GDM. A recent multinational, epidemiologic study showed the risk of adverse maternal fetal and neonatal outcomes rises in direct relation to the mother's glucose level.[16] This study, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, influenced the new guidelines that state that all women should be tested for GDM between 24 and 28 weeks using a 75-g OGTT.[16]

The ingestion of glucose is followed by a venous blood sample for glucose concentration at 1- and 2-hour intervals (ADA). If the plasma glucose level is greater than 92 mg/dL (5.1 mmol/L) fasting, 180 (10.0 mmol/L) at 1 hour or 153 mg/dL (8.5 mmol/L) at 2 hours, a diagnosis of GDM is made (Table 50.4). These new standards will most likely cause a significant increase in the reported number of women with GDM but will support improved glycemic control.[16] Women who have

TABLE 50.4 DIAGNOSIS OF GESTATIONAL DM WITH A 75-g GLUCOSE LOAD

BASELINE AND TIME AFTER ADMINISTRATION OF 75-g GLUCOSE LOAD	PLASMA GLUCOSE LEVEL, mg/dL (mmol/L)
Fasting	92 (5.1)
1 hour	180 (10.0)
2 hours	153 (8.5)

As of 2010, only one venous sample must be met or exceeded for a diagnosis of gestational diabetes. The test should be done in the morning after an overnight fast of between 8 and 14 hours and after at least 3 days of unrestricted diet (>150 g carbohydrate/day) and unlimited physical activity.
Developed from data in American Diabetes Association. (2013). Standards of medical care in diabetes-2013. *Diabetes Care* 36(Suppl. 1), S11–S66.

risk factors for diabetes should be tested at their first prenatal visit and would then be classified as type 2 diabetes if indicated.[16] Diagnosis and careful medical management are essential because women with GDM are at higher risk for complications of pregnancy, mortality, and fetal abnormalities. Fetal abnormalities include macrosomia (*i.e.*, large body size), hypoglycemia, hypocalcemia, polycythemia, and hyperbilirubinemia.[16]

Treatment. Treatment of GDM includes close observation of mother and fetus because even mild hyperglycemia has been shown to be detrimental to the fetus.[17] Maternal fasting and postprandial blood glucose levels should be measured regularly. Fetal surveillance depends on the degree of risk for the fetus. The frequency of growth measurements and determinations of fetal distress depends on available technology and gestational age. All women with GDM require nutritional guidance because nutrition is the cornerstone of therapy. The nutrition plan should provide the necessary nutrients for maternal and fetal health, result in normoglycemia and proper weight gain, and prevent ketosis.[2] Not all women are able to maintain normoglycemia with a nutrition plan alone. For those who need additional support, medication may be warranted. Insulin has long been the treatment of choice when endogenous insulin production is inadequate.[2] In addition, the oral agent glyburide (Glynase, Micronase, Diabeta) is now deemed safe for use in GDM.[17] Self-monitoring of blood glucose levels is essential.

Women with GDM have a 35% to 65% risk of developing type 2 diabetes within 20 years of their pregancy.[1] Predictors of future diabetes or prediabetes include maternal obesity, elevated FPG on OGTT, and family history. Women in whom GDM is diagnosed should be followed after delivery to detect diabetes early in its course.[8]

Clinical Manifestations of Diabetes Mellitus

DM may have a rapid or an insidious onset. In type 1 diabetes, signs and symptoms often arise suddenly. Type 2 diabetes usually develops more insidiously, often existing for years without detection. Its presence may be detected during a routine medical examination or when a person seeks medical care for other reasons.

The most commonly identified signs and symptoms of diabetes are referred to as the *three polys*:

1. Polyuria (*i.e.*, excessive urination)
2. Polydipsia (*i.e.*, excessive thirst)
3. Polyphagia (*i.e.*, excessive hunger)

These three symptoms are closely related to the hyperglycemia and glycosuria of diabetes. Glucose is a small, osmotically active molecule. When blood glucose levels are sufficiently elevated, the amount of glucose filtered by the glomeruli of the kidney exceeds the amount that can be reabsorbed by the renal tubules. This results in glycosuria accompanied by large losses of water in the urine.[3] Thirst results from the intracellular dehydration that occurs as blood glucose levels rise and water is pulled out of body cells, including those in the hypothalamic thirst center.[3] This early symptom may be easily overlooked in people with type 2 diabetes, particularly in those who have had a gradual increase in blood glucose levels. Polyphagia is usually not present in people with type 2 diabetes. In type 1 diabetes, it probably results from cellular starvation and the depletion of cellular stores of carbohydrates, fats, and proteins.[11]

Weight loss despite normal or increased appetite is a common occurrence in people with uncontrolled type 1 diabetes. The cause of weight loss is twofold. First, loss of body fluids results from osmotic diuresis. Vomiting may exaggerate the fluid loss in ketoacidosis. Second, body tissue is lost because the lack of insulin forces the body to use its fat stores and cellular proteins as sources of energy.[11] In terms of weight loss, there is often a marked difference between type 2 diabetes and type 1 diabetes. Weight loss is a frequent phenomenon in people with uncontrolled type 1 diabetes, whereas many people with uncomplicated type 2 diabetes often have problems with obesity. Despite this fact, those with undiagnosed type 2 diabetes may experience unexplained weight loss because circulating insulin is not being utilized, leading to the depletion of energy sources.[12]

Other signs and symptoms of hyperglycemia include recurrent blurred vision, fatigue, and skin infections.[1] In type 2 diabetes, these are often the symptoms that prompt a person to seek medical treatment. Blurred vision develops as the lens and retina are exposed to hyperosmolar fluids. Lowered plasma volume produces weakness and fatigue. Chronic skin infections can occur and are more common in people with type 2 diabetes. Hyperglycemia and glycosuria favor the growth of yeast organisms.[9] *Candida* infections are common initial complaints in women with diabetes.

Diagnostic Tests

The diagnosis of DM is confirmed through the use of laboratory tests that measure blood glucose levels (see Table 50.2). Testing for diabetes should be considered in all people 45 years of age and older.[8] Testing should be considered at a younger

age in people who are obese, have a first-degree relative with diabetes, are members of a high-risk group, have delivered an infant weighing more than 9 lb or been diagnosed with GDM, have hypertension or hyperlipidemia, or have met the criteria for IGT or IFG (*i.e.*, prediabetes) on previous testing.[8]

Blood Tests

Blood glucose measurements are used in both the diagnosis and management of diabetes. Diagnostic tests include the FPG, casual plasma glucose, and the glucose tolerance test. Glycosylated hemoglobin (A1C, previously termed HbA_{1c}) was added to the list of diagnostic test for diabetes in 2009.[8] Previously, A1C had been used only as measure of glucose control over time. Laboratory and capillary or finger-stick glucose tests are used for glucose management in people with diagnosed diabetes. Table 50.5 lists A1C values with correlations of mean plasma glucose levels. People with diabetes should be knowledgeable about their A1C value and the correlation and associations with long-term glycemic control.

Fasting Blood Glucose Test. The FPG has long been the preferred diagnostic test when a fasting blood sample is available.[8] Glucose levels are measured after food has been withheld for at least 8 hours. An FPG level below 100 mg/dL (5.6 mmol/L) is considered normal (see Table 50.2). A level between 100 and 125 mg/dL (5.6 and 6.9 mmol/L) is significant and is defined as impaired fasting glucose. If the FPG level is 126 mg/dL (7.0 mmol/L) diabetes is diagnosed.[5,8]

Casual Blood Glucose Test. A casual plasma glucose is one that is done without regard to the time of the last meal. A casual plasma glucose concentration that is unequivocally elevated (≥200 mg/dL [11.1 mmol/L]) in the presence of classic symptoms of diabetes such as polydipsia, polyphagia, polyuria, and blurred vision is diagnostic of DM at any age.[5,8]

Oral Glucose Tolerance Test. The OGTT is an important screening test for diabetes. The test measures the body's ability to store glucose by removing it from the blood. In men and women, the test measures the plasma glucose response to 75 g of concentrated glucose solution at selected intervals, usually 1 and 2 hours. In people with normal glucose tolerance, blood glucose levels return to normal within 2 to 3 hours after ingestion of a glucose load, in which case it can be assumed that sufficient insulin is present to allow glucose to leave the blood and enter body cells. Because a person with diabetes lacks the ability to respond to an increase in blood glucose by releasing adequate insulin to facilitate storage, blood glucose levels rise above those observed in normal people and remain elevated for longer periods (see Table 50.2).[3]

TABLE 50.5 CORRELATION BETWEEN HEMOGLOBIN A1C LEVEL AND MEAN PLASMA GLUCOSE LEVELS

HEMOGLOBIN A1C (%)	MEAN PLASMA GLUCOSE, mg/dL (mmol/L)
6	126 (7)
7	154 (8.6)
8	183 (10.2)
9	212 (11.8)
10	240 (13.4)
11	269 (14.9)
12	298 (16.5)

Adapted from American Diabetes Association. (2011). Standards of medical care in diabetes-2011. *Diabetes Care* 34(Suppl. 1), S11–S61.

Capillary Blood Glucose Monitoring. Technological advances have provided the means for monitoring blood glucose levels by using a drop of capillary blood. This procedure has provided health professionals with a rapid and economical means for monitoring blood glucose and has given people with diabetes a way of maintaining near-normal blood glucose levels through self-monitoring of blood glucose. These methods use a drop of capillary blood obtained by pricking the finger or forearm with a special needle or small lancet. The drop of capillary blood is placed on or absorbed by a reagent strip, and glucose levels are determined electronically using a glucose meter. Alternate site testing, using locations other than fingertips, should be cautioned at time of suspected hypoglycemia due to wide discordance in values at times of rapid glucose fluctuations.[18]

Laboratory tests that use plasma for measurement of blood glucose give results that are 10% to 15% higher than the finger-stick method, which uses whole blood.[18] Most monitors approved for home use calibrate blood glucose readings to plasma values for easier comparison to lab values. Continuous glucose monitoring systems are becoming available to fine-tune glucose management. The various systems have small catheters implanted in the subcutaneous tissue to provide frequent samples. Endocrine centers are increasingly using this technology in selected people to achieve optimal glycemic management. The variety and accuracy of these systems is continually improving. However, finger-stick glucose monitoring remains the standard of care.[18]

Glycated Hemoglobin Testing. Glycated hemoglobin, also referred to as glycohemoglobin, glycosylated hemoglobin, HbA_{1c}, or *A1C* (the preferred term), is a term used to describe hemoglobin into which glucose has been incorporated. Hemoglobin normally does not contain glucose when it is released from the bone marrow. During its 120-day life span in the red blood cell, hemoglobin normally becomes glycated to form hemoglobins A_{1a} and A_{1b} (2% to 4%), and A1C (4% to 6%). Because glucose entry into red blood cells is not insulin dependent, the rate at which glucose becomes attached to the hemoglobin molecule depends on blood glucose levels. Glycosylation is essentially irreversible, and the *level of A1C present in the blood provides an index of blood glucose levels over the previous 6 to 12 weeks*.[9] In uncontrolled diabetes or diabetes with hyperglycemia, there is an increase in the level of A1C.

The ADA recommends initiating corrective measures for A1C levels greater than 7%. However, the goal has been redefined as lowering the A1C to less than 7.0%, or even achieving normal glycemic levels of less than 6.0%.[8] Recommendations to people regarding optimal control take into account many factors including any associated risk of injury. A1C has been a key indicator for long-term control as it has strong predictive value for complications of diabetes. Many practitioners welcome its more recent inclusion as a diagnostic tool for diabetes.

Urine Tests

The ease, accuracy, and convenience of self-administered blood glucose monitoring techniques have made urine testing for glucose obsolete for most people with diabetes. These tests only reflect urine glucose levels and are influenced by such factors as the renal threshold for glucose, fluid intake and urine concentration, urine testing methodologies, and some drugs. It is recommended that all people with diabetes self-monitor their blood glucose. Urine ketone determinations remain an important part of monitoring diabetic control, particularly in people with type 1 diabetes who are at risk for development of ketoacidosis, and in pregnant diabetic women to check the adequacy of nutrition and glycemic control.[11]

Emily and her family will need to learn how and when to check urine testing for ketones as well as using a finger-stick machine to monitor blood glucose levels.

Treatment

The desired outcome of glycemic control in both type 1 and type 2 diabetes is normalization of blood glucose as a means of preventing short- and long-term complications. Treatment plans involve medical nutrition therapy, exercise, and antidiabetic agents. People with type 1 diabetes require insulin therapy from the time of diagnosis. Weight loss and dietary management may be sufficient to control blood glucose levels in some people with type 2 diabetes who adopt lifestyle changes long term. However, most require follow-up care because insulin secretion from the beta cells may decrease or insulin resistance may persist or worsen, in which case oral antidiabetic agents are prescribed.

Among the methods used to achieve these treatment goals are diabetes self-management education (DSME) and problem solving. Individual treatment goals should take into account the person's age and other disease conditions, the person's capacity to understand and carry out the treatment regime, and socioeconomic factors that might influence compliance with the treatment plan.[12] Long-term glycemic management is critical to the delay and prevention of diabetes complications and is heavily dependent on the person's knowledge of the multiple components of care.

Dietary Management

Dietary management is a founding component of diabetes care. The term *medical nutrition therapy*, which was introduced in 1994 by the ADA, is defined as the use of specific nutrition services to treat an illness, injury, or condition and involves both the assessment of the nutrition status and the treatment measure, including nutrition therapy, counseling, and use of specialized nutritional supplements.[2] Previously considered rigid and complex, today's medical nutrition therapy (MNT) is more evidence-based and individualized. The diabetic diet has undergone marked changes over the years, particularly in the recommendations for distribution of calories among carbohydrates, proteins, and fats. There is no longer a specific diabetic or ADA diet but rather a dietary prescription based on nutrition assessment and treatment goals. A coordinated team effort, including the person with diabetes, is needed to individualize the nutrition plan.

Goals and principles of diet therapy differ between type 1 and type 2 diabetes and between lean and obese people. Integral to diabetes management is a prescribed plan for nutrition therapy.[2] Therapy goals include maintenance of near-normal blood glucose levels, achievement of optimal lipid levels, adequate calories to maintain and attain reasonable weights, prevention and treatment of chronic diabetes complications, and improvement of overall health through optimal nutrition. Initial guidelines may include 45% to 60% carbohydrate, 20% to 35% fat, and 10% to 20% protein.[2]

For a person with type 1 diabetes, the usual food intake is assessed and used as a basis for adjusting insulin therapy to fit with the person's lifestyle. Eating consistent amounts and types of food at specific and routine times are encouraged. Home blood glucose provide for immediate feedback on nutritional intake, glycemic response, and influence of physical activity.[19] For those with type 1 diabetes, improvements in insulin regimes and increasing use of insulin pumps allow for more flexibility with meals.[18]

Most people with type 2 diabetes are overweight. Nutrition therapy goals focus on achieving glucose, lipid, and blood pressure goals, and weight loss if indicated. Mild to moderate weight loss (5% to 10% of total body weight) has been shown to improve diabetes control, even if desirable weight is not achieved.[20] Dietary considerations for cardiac risk factors also play a role in individualizing care for those with type 2 diabetes. National dietary guidelines for saturated fat, sodium, and fiber also play a role in dietary planning for those with diabetes.[18] The registered dietitian plays an essential role in the diabetes care team and is able to select from a variety of methods such as carbohydrate counting, food exchanges, healthy food choices, glycemic index, and total available glucose to tailor the meal plan to meet individual needs. Simpler recommendations have been associated with improved client understanding and dietary adherence. Carbohydrate counting uses product label information that is easily available to people with diabetes.[2] Regardless of food source, total grams of carbohydrate are counted, placing an emphasis on the nutrient that most affects blood glucose control.

Emily and her family should work closely with a registered dietitian throughout her lifespan to maximize understanding regarding the vital role of nutrition for her health. Today's approach to flexible, individualized meal planning will allow Emily to enjoy a normal healthy diet rather than the need for a specialized and rigid regime, which alienates her from her peers.

MNT is also important in preventing, or at least slowing, the development of complications. Because diabetes is a risk factor for cardiovascular disease, it is recommended that less than 7% of daily calories should be obtained from saturated fat and that dietary cholesterol be limited to 200 mg or less, and intake of trans fats minimized.[2] Periodic fasting lipid panels may identify concomitant lipid disorders. As associated conditions of diabetes develop, MNT continues to be a key component of optimizing outcomes. Issues such as hyperlipidemia, coronary artery disease, renal insufficiency, neuropathy, and hypertension require additional considerations focused on sodium intake and other nutrients.

Exercise

The benefits of exercise are numerous in relation to diabetes and associated conditions. Cardiovascular fitness and psychological well-being are desirable for all people but for many people with type 2 diabetes, the benefits of exercise include a decrease in body fat, better weight control, and improvement in insulin sensitivity.[19] Exercise is so important in diabetes management that a planned program of regular exercise usually is considered an integral part of the therapeutic regimen for every person with diabetes.[19] In general, sporadic exercise has only transient benefits. A regular exercise or training program is the most beneficial; it is better for cardiovascular conditioning and can maintain a muscle–fat ratio that enhances peripheral insulin receptivity.[19]

In people with diabetes, the beneficial effects of exercise are accompanied by an increased risk of hypoglycemia, especially for those taking insulin injections. Although muscle uptake of glucose increases significantly, the ability to maintain blood glucose levels is hampered by failure to suppress the absorption of injected insulin and activate the counter-regulatory mechanisms that maintain blood glucose.[19] Not only is there an inability to suppress insulin levels, but insulin absorption may increase. This increased absorption is more pronounced when insulin is injected into the subcutaneous tissue of the exercised muscle, but it occurs even when insulin is injected into other body areas. Even after exercise ceases, insulin's lowering effect on blood glucose continues. In some people with type 1 diabetes, the symptoms of hypoglycemia occur several hours after cessation of exercise, perhaps because subsequent insulin doses (in people using multiple daily insulin injections) are not adjusted to accommodate the exercise-induced decrease in blood glucose.[19] The cause of hypoglycemia in people who do not administer a subsequent insulin dose is unclear. It may be related to the fact that the liver and skeletal muscles increase their uptake of glucose after exercise as a means of replenishing their glycogen stores, or that the liver and skeletal muscles are more sensitive to insulin during this time.[19] People with diabetes should be aware that delayed hypoglycemia can occur after exercise and that they may need to alter their diabetes medication dose, their carbohydrate intake, or both.

Although of benefit to people with diabetes, exercise must be weighed on the risk–benefit scale. Before beginning an exercise program, persons with diabetes should undergo an appropriate evaluation for macrovascular and microvascular disease.[19] The goal of exercise is safe participation in activities consistent with a person's lifestyle. As with nutrition guidelines, exercise recommendations need to be individualized. Each person should have goals, which include amount of exercise, duration of exercise, blood glucose levels before initiation of exercise, and problem-solving skills. Considerations include the potential for hypoglycemia, hyperglycemia, ketosis, cardiovascular ischemia and arrhythmias (particularly silent ischemic heart disease), exacerbation of proliferative retinopathy, and lower extremity injury.[19] For people with type 1 diabetes who exercise during periods of poor control (*i.e.*, when blood glucose is elevated, exogenous insulin levels are low, and ketonemia exists), blood glucose and ketones rise to even higher levels because the stress of exercise is superimposed on preexisting insulin deficiency and increased counter-regulatory hormone activity.[19]

Oral and Injectable Antidiabetic Medications

The last few years have seen not only new medications for diabetes treatment, but new categories of medications. No longer are the choices oral agents or insulin. Medications to treat diabetes now include newer injectable antidiabetic agents (*e.g.*, amylin analogs and glucagon-like peptide-1 [GLP-1] analogs).[6] Because people with type 1 diabetes are deficient in insulin, they are in need of exogenous insulin replacement therapy from the start.[11] People with type 2 diabetes can have increased hepatic glucose production; decreased peripheral utilization of glucose; decreased utilization of ingested carbohydrates; and, over time, impaired insulin secretion and excessive glucagon secretion from the pancreas (Fig. 50.7).[12] The antidiabetic agents used in the treatment of type 2 diabetes attack each one of these areas and sometimes all.[6] If good glycemic control cannot be achieved with one or a combination of antidiabetic agents, insulin can be added or used by itself.

Oral antidiabetic agents fall into five categories: (1) insulin secretagogues (*i.e.*, sulfonylureas, repaglinide, and nateglinide), (2) biguanides, (3) α-glucosidase inhibitors, (4) dipeptidyl peptidase-4 (DPP-4) enzyme inhibitors, (5) thiazolidinediones (TZDs) (Table 50.6). In addition, a GLP-1 agonist and amylin agonist in injectable formulations are now widely used.

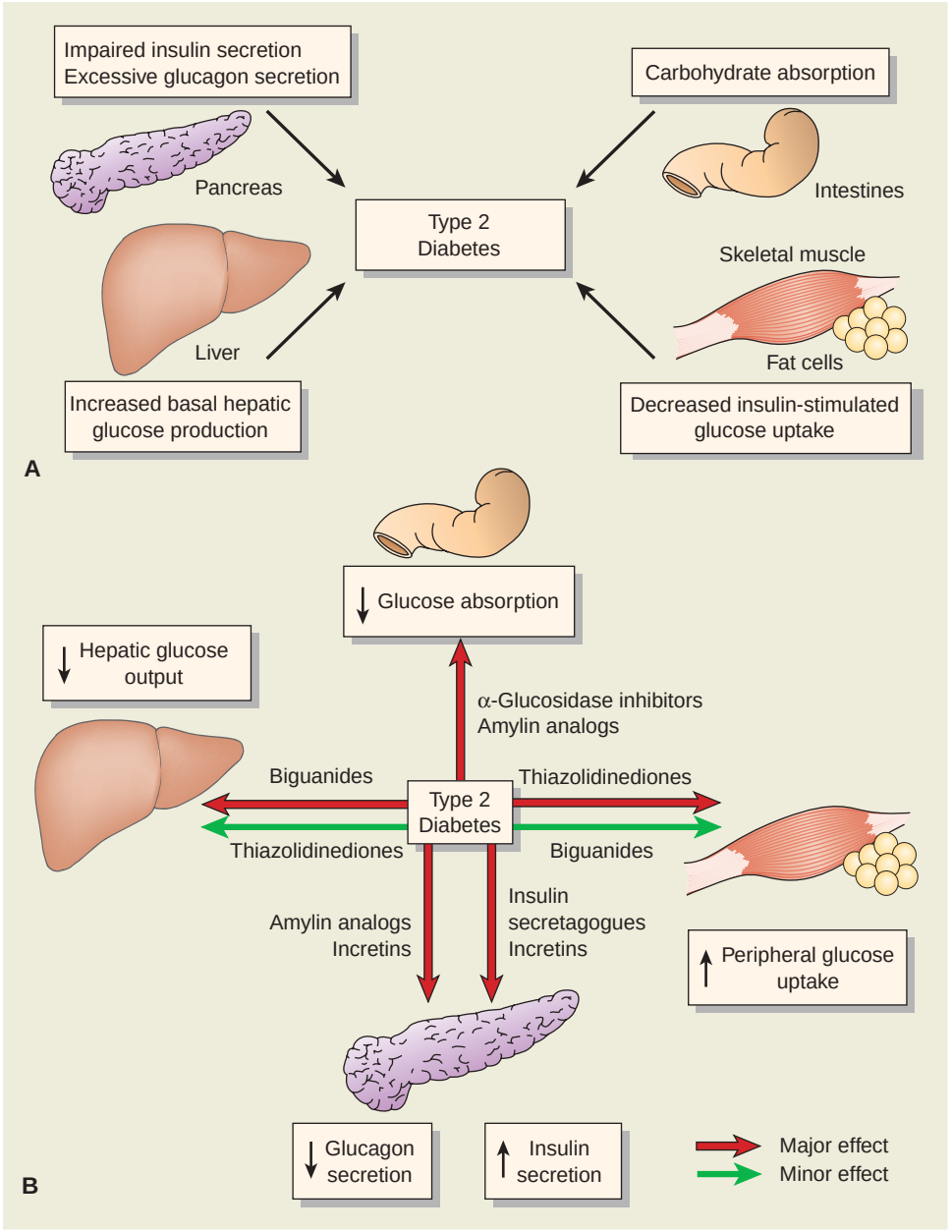


FIGURE 50.7 • (**A**) Mechanisms of elevated blood glucose in type 2 DM. (**B**) Action sites of hypoglycemic agents and mechanisms of lowering blood glucose in type 2 diabetes. The incretins are the DPP-4 inhibitors and GLP-1 agonists.

Insulin Secretagogues: Sulfonylureas. The sulfonylureas were discovered accidentally in 1942, when scientists noticed that one of the sulfonamide drugs being developed at the time caused hypoglycemia. These drugs reduce blood glucose by stimulating the release of insulin from beta cells in the pancreas. These agents are effective only when some residual beta cell function remains. The sulfonylureas act by binding to a high-affinity sulfonylurea receptor on the beta cell that is linked to an ATP-sensitive potassium channel.[6]

The sulfonylureas are used in the treatment of type 2 diabetes and cannot be substituted for insulin in people with type 1 diabetes, who have an absolute insulin deficiency. The sulfonylureas traditionally are grouped into first- and second-generation agents (see Table 50.6). These agents differ in dosage and duration of action. The second-generation drugs (*e.g.*, glyburide, glipizide, glimepiride) are considerably more potent that the first-generation drugs and are more widely prescribed than the first-generation agents.[6]

Because the sulfonylureas increase insulin levels and the rate at which glucose is removed from the blood, it is important to recognize that they can cause hypoglycemic reactions. This problem is more common in elderly people with impaired hepatic and renal function who take the longer-acting sulfonylureas. At one time sulfonylureas were a mainstay of treatment for type 2 diabetes. With the increase in approaches to pharmacologic treatment of diabetes, agents with less threat of hypoglycemia may be more desirable.[15]

Insulin Secretagogues: Repaglinide and Nateglinide. Repaglinide and nateglinide are nonsulfonylurea insulin secretagogues that require the presence of glucose for their main action. These agents exert their action by

Acue Complications of Diabetes

The three major acute complications of diabetes are DKA, hyperosmolar hyperglycemic state (HHS), and hypoglycemia. All are life-threatening conditions that demand immediate recognition and treatment. These complications account for a significant number of hospitalizations and consumption of health care resources.[26]

Diabetic Ketoacidosis

DKA most commonly occurs in a person with type 1 diabetes, in whom the lack of insulin leads to mobilization of fatty acids from adipose tissue because of the unsuppressed adipose cell lipase activity that breaks down triglycerides into fatty acids and glycerol.[27] The increase in fatty acid levels leads to ketone production by the liver (Fig. 50.9). It can occur at the onset of the disease, often before the disease has been diagnosed.

Stress increases the release of gluconeogenic hormones and predisposes the person to the development of ketoacidosis.[27] DKA is often preceded by physical or emotional stress, such as infection, pregnancy, or extreme anxiety. Recent evidence suggests the hyperglycemia is associated with a severe inflammatory state.[26] In clinical practice, ketoacidosis also occurs with the omission or inadequate use of insulin. One example of this is a teenager with type 1 diabetes who decides to stop using insulin.

Etiology and Pathogenesis. The three major metabolic derangements in DKA are hyperglycemia, ketosis, and metabolic acidosis. The definitive diagnosis of DKA consists of hyperglycemia (blood glucose levels >250 mg dL [13.8 mmol/L]), low serum bicarbonate (<15 mEq/L [15 mmol/L]), and low pH

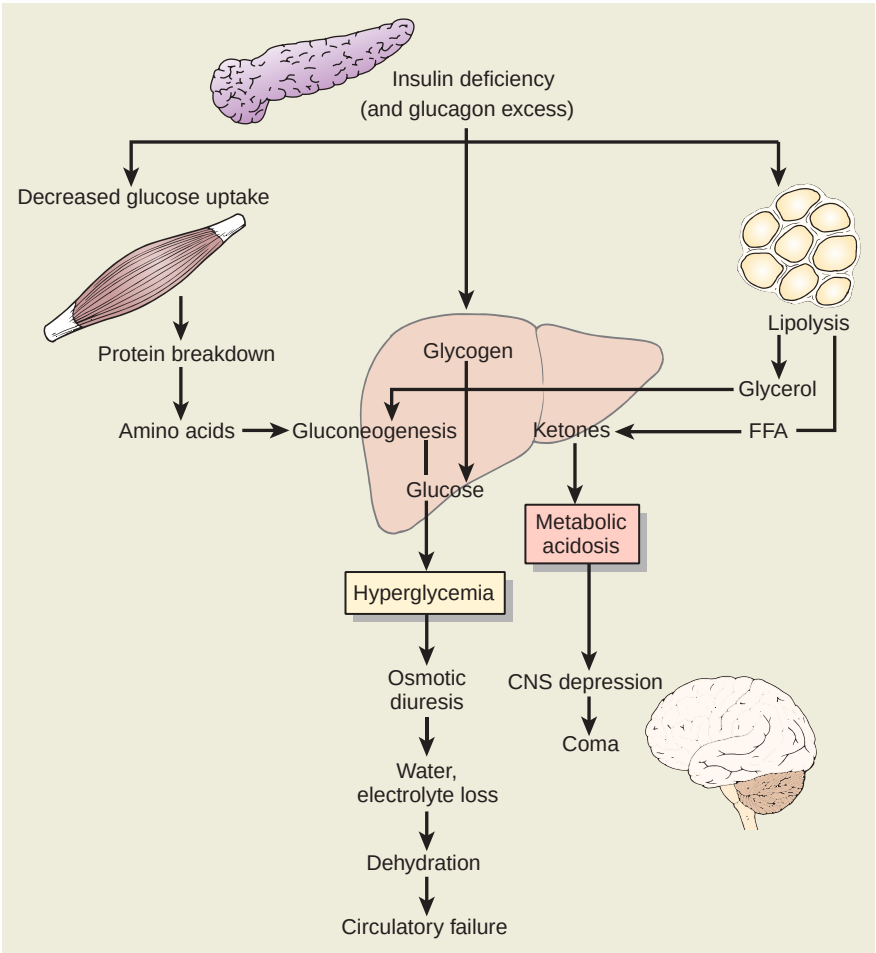


FIGURE 50.9 • Mechanisms of DKA. DKA is associated with very low insulin levels and extremely high levels of glucagon, catecholamines, and other counter-regulatory hormones. Increased levels of glucagon and the catecholamines lead to mobilization of substrates for gluconeogenesis and ketogenesis by the liver. Gluconeogenesis in excess of that needed to supply glucose for the brain and other glucose-dependent tissues produces a rise in blood glucose levels. Mobilization of free fatty acids (FFA) from triglyceride stores in adipose tissue leads to accelerated ketone production and ketosis. (CNS, central nervous system.)

(<7.3), with ketonemia (positive at 1:2 dilution) and moderate ketonuria.[26] Hyperglycemia leads to osmotic diuresis, dehydration, and a critical loss of electrolytes. Hyperosmolality of extracellular fluids from hyperglycemia leads to a shift of water and potassium from the intracellular to the extracellular compartment. Extracellular sodium concentration is frequently low or normal despite enteric water losses because of the intracellular–extracellular fluid shift.[26] This dilutional effect is referred to as *pseudohyponatremia*.[9] Serum potassium levels may be normal or elevated, despite total potassium depletion resulting from protracted polyuria and vomiting. Metabolic acidosis is caused by the excess ketoacids that require buffering by bicarbonate ions. This leads to a marked decrease in serum bicarbonate levels. The severity of DKA is classified on the severity of the metabolic acidosis.[26]

Clinical Manifestations. A day or more of polyuria, polydipsia, nausea, vomiting, and marked fatigue, with eventual stupor that can progress to coma commonly precedes DKA. Abdominal pain and tenderness may be experienced without abdominal disease.[26] The breath has a characteristic fruity smell because of the presence of the volatile ketoacids.[27] Hypotension and tachycardia may be present because of a decrease in blood volume. A number of the signs and symptoms that occur in DKA are related to compensatory mechanisms. The heart rate increases as the body compensates for a decrease in blood volume, and the rate and depth of respiration increase (*i.e.*, Kussmaul respiration) as the body attempts to prevent further decreases in pH.[26]

Treatment. The goals in treating DKA are to improve circulatory volume and tissue perfusion, decrease blood glucose, correct the acidosis, and correct electrolyte imbalances.[26,27] These objectives are usually accomplished through the administration of insulin and intravenous fluid and electrolyte replacement solutions. Because insulin resistance accompanies severe acidosis, low-dose insulin therapy is used.[26] An initial loading dose of regular insulin is often given intravenously, followed by continuous low-dose infusion. Frequent laboratory tests are used to monitor blood glucose and serum electrolyte levels and to guide fluid and electrolyte replacement. It is important to replace fluid and electrolytes and correct pH while bringing the blood glucose concentration to a normal level. Too rapid a drop in blood glucose may cause hypoglycemia. A sudden change in the osmolality of extracellular fluid can also occur when blood glucose levels are lowered too rapidly, and this can cause cerebral edema, more common in children than in adults.[27] Serum potassium levels often fall as acidosis is corrected and potassium moves from the extracellular into the intracellular compartment. Thus, it may be necessary to add potassium to the intravenous infusion. Identification and treatment of the underlying cause, such as infection, are also important. The most common complications from overtreatment of DKA are hypoglycemia and hypokalemia.[26] Increasing use of evidence-based order sets have supported safer care of DKA in the acute setting.

Emily Toronto exhibited all the criteria for DKA, including hyperglycemia (650 mg/dL), ketosis, and metabolic acidosis with an arterial blood gas of pH = 7.29, pCO_2 = 42 mm Hg, and HCO_3 = 10 mEq/L. Her hyperglycemia, polydipsia, and vomiting have caused dehydration. Her immediate needs are hydration with correction of electrolyte imbalance, treatment of hyperglycemia with insulin, and close monitoring of vital signs and laboratory values. Once she is stabilized it will be important to educate the family; the risk of DKA will continue for Emily in certain circumstances, but can often be prevented.

Hyperosmolar Hyperglycemic State

HHS is characterized by hyperglycemia (blood glucose >600 mg/dL [33.3 mmol/L]), hyperosmolarity (plasma osmolarity >320 mOsm/L) and dehydration, the absence of ketoacidosis, and depression of the sensorium.[28] HHS may occur in various conditions, including type 2 diabetes, acute pancreatitis, severe infection, myocardial infarction, and treatment with oral or parenteral nutrition solutions.[27] It is seen most frequently in people with type 2 diabetes.

Etiology and Pathogenesis. A partial or relative insulin deficiency may initiate the syndrome by reducing glucose utilization while inducing hyperglucagonemia and increasing hepatic glucose output. With massive glycosuria, obligatory water loss occurs.[26] Dehydration is usually more severe than DKA. As the plasma volume contracts, renal insufficiency develops and the resultant limitation of renal glucose losses leads to increasingly higher blood glucose levels and severity of the hyperosmolar state.[26] In hyperosmolar states, the increased serum osmolarity has the effect of pulling water out of body cells, including brain cells. The condition may be complicated by thromboembolic events arising because of the high serum osmolality.

Clinical Manifestations and Treatment. The most prominent manifestations are weakness, dehydration, polyuria, neurologic signs and symptoms, and excessive thirst. Neurologic signs including hemiparesis, seizures, and coma can occur.[26] The onset of HHS can evolve over days to weeks but the onset of neurologic symptoms, especially in older people, may be mistaken for a stroke.

Successful treatment of HHS requires correction of dehydration, hyperglycemia, electrolyte imbalance, and frequent patient monitioring.[26] The treatment of HHS requires judicious medical observation and care as water moves back into brain cells, posing a threat of cerebral edema.[27] Extensive potassium losses that also have occurred during the diuretic phase of the disorder require correction. Because many people with HHS have coexisting chronic conditions, the identification of

comorbid precipitating events is important to the treatment of this dangerous condition.[26]

Hypoglycemia

Hypoglycemia is generally defined as cognitive impairment with a blood glucose concentration of less than 60 mg/dL.[2] It occurs most commonly in people treated with insulin injections, but prolonged hypoglycemia can also result from some oral hypoglycemic agents.

Etiology and Pathogenesis. There are many factors that can precipitate hypoglycemia in a person with type 1 diabetes, including error in insulin dose, failure to eat, increased exercise, decreased insulin need after removal of a stress situation, medication changes, and a change in insulin injection site.[21] Alcohol decreases liver gluconeogenesis, and people with diabetes need to be cautioned about its potential for causing hypoglycemia, especially if it is consumed in large amounts or on an empty stomach.[28]

Clinical Manifestations. Hypoglycemia usually has a rapid onset and progression of symptoms. The signs and symptoms of hypoglycemia can be divided into two categories: (1) those caused by altered cerebral function, and (2) those related to activation of the autonomic nervous system.[28] Because the brain relies on blood glucose as its main energy source, hypoglycemia produces behaviors related to altered cerebral function. Headache, difficulty in problem solving, disturbed or altered behavior, coma, and seizures may occur. At the onset of the hypoglycemic episode, activation of the parasympathetic nervous system often causes hunger.[21] The initial parasympathetic response is followed by activation of the sympathetic nervous system; this causes anxiety, tachycardia, sweating, and constriction of the skin vessels (*i.e.*, the skin is cool and clammy).[21]

The signs and symptoms of hypoglycemia are highly variable, and not everyone manifests all or even most of the symptoms. The signs and symptoms are particularly variable in children and in older adults. Older adults may not display the typical autonomic responses associated with hypoglycemia but frequently develop signs of impaired function of the central nervous system, including mental confusion. Some people develop hypoglycemic unawareness. Unawareness of hypoglycemia should be suspected in people who do not report symptoms when their blood glucose concentrations are less than 50 to 60 mg/dL (2.8 to 3.3 mmol/L). This occurs most commonly in people who have a longer duration of diabetes and A1C levels within the normal range.[28] Some medications, such as β-adrenergic blocking drugs, interfere with the sympathetic response normally seen in hypoglycemia. If hypoglycemia occurs with α-glucosidase inhibitors, it should be treated with glucose (dextrose) and not sucrose (table sugar), whose breakdown may be blocked by the action of the α-glucosidase inhibitors.[16]

Treatment. The most effective treatment of an insulin reaction is the immediate administration of 15 to 20 g of glucose in a concentrated carbohydrate source, which can be repeated as necessary. Monosaccharides such as glucose, which can be absorbed directly into the bloodstream, work best.[2] Complex carbohydrates can be administered after the acute reaction has been controlled to sustain blood glucose levels. It is important not to overtreat hypoglycemia and cause hyperglycemia. This is supported by testing the blood glucose 15 minutes following the ingestion of glucose, and if necessary, repeating the 15-g concentrated carbohydrate (15/15 rule).

Alternative methods for increasing blood glucose may be required when the person having the reaction is unconscious or is unable to swallow. This is categorized as severe hypoglycemia and requires the intervention of another person. Glucagon may be given intramuscularly or subcutaneously. Glucagon acts by hepatic glycogenolysis to raise blood sugar.[11] A small amount of glucose gel (available in most pharmacies) may be inserted into the buccal pouch when glucagon is unavailable. In situations of severe or life-threatening hypoglycemia, it may be necessary to administer glucose (20 to 50 mL of a 50% solution) intravenously.[28]

Counter-Regulatory Mechanisms and the Somogyi Effect and Dawn Phenomenon

The Somogyi effect describes a cycle of insulin-induced posthypoglycemic episodes.[29] In 1924, Joslin et al. noticed that hypoglycemia was associated with alternate episodes of hyperglycemia. In people with diabetes, insulin-induced hypoglycemia produces a compensatory increase in blood levels of catecholamines, glucagon, cortisol, and growth hormone.[29] These counter-regulatory hormones cause blood glucose to become elevated and produce some degree of insulin resistance. The cycle begins when the increase in blood glucose and insulin resistance is treated with larger insulin doses.

Clinically, high blood glucose levels in the morning can complicate medical treatment of diabetes if not fully understood to be a counter-regulatory result of hypoglycemia. The hypoglycemic episode often occurs during the night or at a time when it is not recognized, rendering the diagnosis of the phenomenon more difficult.[29] Without proper evaluation an increase in medication can exacerbate the situation. When a Somogyi situation is suspected, people may be asked to test blood sugars in the middle of the night to identify possible hypoglycemia. The use of continuous insulin sensors, in selected patients, can also help to identify this situation.

The dawn phenomenon is characterized by increased levels of fasting blood glucose or insulin requirements, or both, between 5 and 9 AM without antecedent hypoglycemia (as opposed to the Somogyi).[29] It occurs in people with type 1 or type 2 diabetes. It has been suggested that the dawn phenomenon is not fully understood but has been attributed to an increased rate of insulin clearance, decreased insulin sensitivity, or both.[29] Several hormones such as growth hormone, cortisol, and glucagon have been studied in relation to this phenomenon.[29] The dawn phenomenon has been found to occur in the majority of those with type 1 diabetes. The impact varies

depending on a variety of factors such as blood sugar control and adequacy of counter-regulatory systems.[29] Advances in diabetes care especially the advanced insulin pumps can address varied needs of basal insulin in early morning hours.

Chronic Complications

The chronic complications of diabetes include disorders of the microvasculature (*i.e.*, neuropathies, nephropathies, and retinopathies), disorders of gastrointestinal motility, macrovascular complications (*i.e.*, coronary artery, cerebral vascular, and peripheral vascular disease), and foot ulcers (Fig. 50.10). The level of chronic hyperglycemia is the best-established concomitant factor associated with diabetic complications.[30]

The causes and development of complications in diabetes are not fully understood but may relate to a variety of factors. Excess amounts of sorbitol may alter cellular function.[9,30]

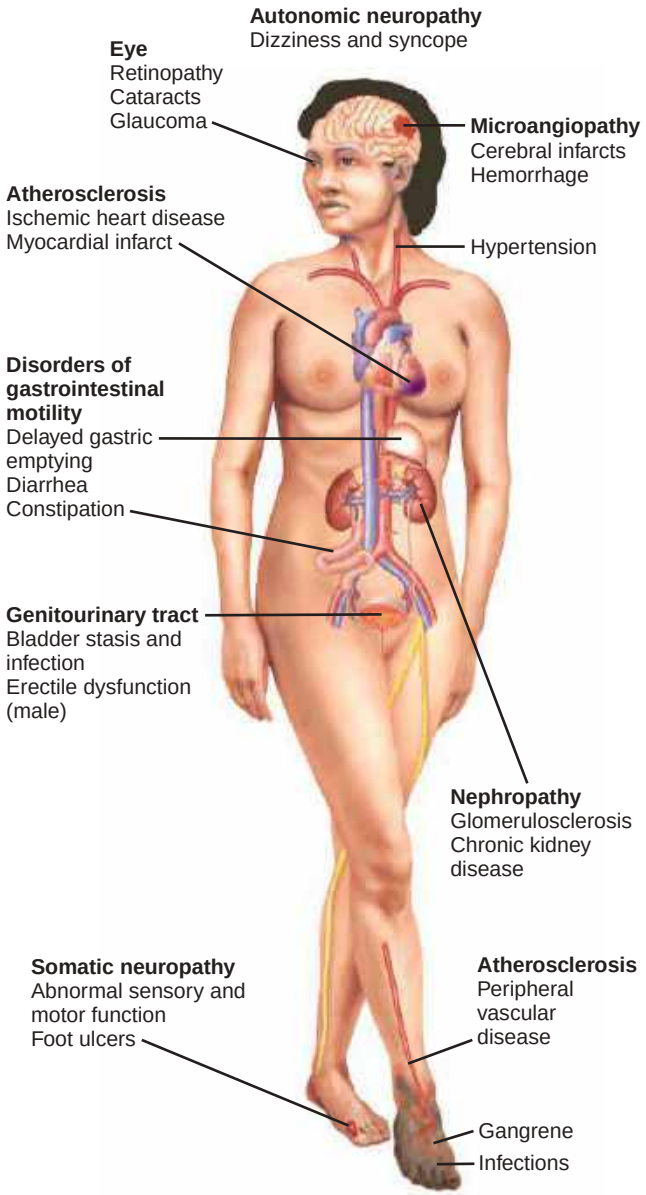


FIGURE 50.10 • Long-term complications of DM.

Abnormal glycoproteins may damage the basement membranes related to eyes, kidneys, and vascular circulation. Tissue oxygenation is believed to be a significant cause of microvascular complications due to a defect in red blood cell function. These abnormalities and others are theorized to cause an increase in free reactive oxygen species (*i.e.*, free radicals) in response to chronic hyperglycemia.[3]

The Diabetes Control and Complications Trial (DCCT), which was conducted with 1441 patients with type 1 diabetes, demonstrated that the incidence of retinopathy, nephropathy, and neuropathy can be reduced by intensive diabetic treatment.[31] Similar results have been demonstrated by the United Kingdom Prospective Diabetes Study (UKPDS) in 5000 people with type 2 diabetes.[32]

Recent studies have also determined the positive benefits of excellent glycemic control during hospitalization, surgery, and acute illness states.[33] All people with diabetes admitted to acute health care facilities need to be identified and have an order for blood glucose monitoring. Goals for blood glucose control for hospitalized people are as close to 110 mg/dL (5.6 mmol/L) as possible, and generally less than 140 mg/dL (7.8 mmol/L) for critically ill people and generally less than 180 mg/dL (10 mmol/L) for non–critically ill people.[33]

Neuropathies

The risk of neuropathies, along with other chronic complications, has been shown to increase in the presence of long-term hyperglycemia.[31] Symptoms usually become apparent in the second decade of the disease. As the onset of type 2 diabetes often goes undetected, chronic complications can exist at the time of diagnosis. Although the incidence of neuropathies is high among people with diabetes, it is difficult to document exactly how many people are affected by these disorders because of the diversity in clinical manifestations and because the condition may be unrecognized or unreported.[34]

Two types of pathologic changes have been observed in connection with diabetic neuropathies. The first is a thickening of the walls of the nutrient vessels that supply the nerve, leading to the assumption that vessel ischemia plays a major role in the development of these neural changes. The second finding is a segmental demyelinization process that affects the Schwann cell. This demyelinization process is accompanied by a slowing of nerve conduction.

Although there are several methods for classifying the diabetic neuropathies, a simplified system divides them into the somatic and autonomic nervous system neuropathies (Chart 50.4).

Somatic Neuropathy. A distal symmetric polyneuropathy, in which loss of function occurs in a stocking–glove pattern, is the most common form of peripheral neuropathy.[34] Somatic sensory involvement usually occurs first and is usually bilateral and symmetric, and associated with diminished perception of vibration, pain, and temperature, particularly in the lower extremities.[35] In addition to the discomforts associated with the loss of sensory or motor function, lesions in the peripheral nervous system predispose a person with diabetes to other complications. Peripheral neuropathy is often associated with

CHART 50.4 CLASSIFICATION OF DIABETIC NEUROPATHIES

Somatic

Polyneuropathies (bilateral sensory)
- Paresthesias, including numbness and tingling
- Impaired pain, temperature, light touch, two-point discrimination, and vibratory sensation
- Decreased ankle and knee-jerk reflexes

Mononeuropathies
- Involvement of a mixed nerve trunk that includes loss of sensation, pain, and motor weakness

Amyotrophy
- Associated with muscle weakness, wasting, and severe pain of muscles in the pelvic girdle and thigh

Autonomic

Impaired vasomotor function
- Postural hypotension

Impaired gastrointestinal function
- Gastroparesis
- Diarrhea, often postprandial and nocturnal

Impaired genitourinary function
- Paralytic bladder
- Incomplete voiding
- Erectile dysfunction
- Retrograde ejaculation

Cranial nerve involvement
- Extraocular nerve paralysis
- Impaired pupillary responses
- Impaired special senses

the insensate foot.[35] The loss of feeling, touch, sensation, and position sense increases the risk of falling, serious burns, and injuries to the feet.[34] Neuropathy of the lower extremities is associated with 61% of lower extremity amputations and the mortality rate within 5 years after such amputations ranges from 39% to 80%.[35]

Painful diabetic neuropathy involves the somatosensory neurons that carry pain impulses. Treatment of this painful disorder is available with pharmacologic and holistic interventions. Use of varied agents such as antidepressants, anticonvulsants may have side effects that limit their usefulness.[36] In addition to debilitating pain and impaired quality of life, the treatment of peripheral neuropathy and the subsequent interventions related to this complication place a financial burden on health care resources.[37] Loss of income, disability, wound treatment, surgery, infections, prosthetics, and more are associated with this chronic and common complication.

Autonomic Neuropathy. The autonomic neuropathies involve disorders of sympathetic and parasympathetic nervous system function. There may be disorders of vasomotor function, decreased cardiac responses, inability to empty the bladder, and sexual dysfunction.[30] Defects in vasomotor reflexes can lead to dizziness and syncope when the person moves from the supine to the standing position. In the male, disruption of sensory and autonomic nervous system function may cause sexual dysfunction. Diabetes is the leading physiologic cause of erectile dysfunction (ED), and it occurs in both type 1 and type 2 diabetes.[30] The current availability of pharmacologic treatment of ED can offer improved management of this common complication but individually must be appropriately screened due to cardiac implications and other conditions associated with diabetes.

Disorders of Gastrointestinal Motility

Gastrointestinal motility disorders are common in people with long-standing diabetes. Although the pathogenesis of these disorders is poorly understood, neuropathy and metabolic abnormalities secondary to hyperglycemia are thought to play an important role.[30] The symptoms vary in severity and include constipation, diarrhea and fecal incontinence, nausea and vomiting, and upper abdominal discomfort referred to as dyspepsia.

Gastroparesis (delayed emptying of stomach) is commonly seen in persons with diabetes.[30] The disorder is characterized by complaints of epigastric discomfort, nausea, postprandial vomiting, bloating, and early satiety. Erratic blood glucose can occur due to delayed food absorbtion.[30] Diagnostic measures include the use of endoscopy or barium radiography to exclude mechanical obstruction due to peptic ulcer disease or cancer.[5] Management includes the use of prokinetic agents (*e.g.*, metoclopramide, erythromycin) as well as antiemetic agents.[9] Strict glycemic control along with small frequent meals is also advised.[30]

Diarrhea is another common symptom seen mostly in persons with poorly controlled type 1 diabetes and autonomic neuropathy.[30] The pathogenesis is thought to be multifactorial. Diabetic diarrhea is typically intermittent, watery, painless, and nocturnal and may be associated with fecal incontinence or may alternate with constipation.[30] Management includes soluble dietary fiber and the use of antidiarrheal agents (loperamide, diphenoxylate). Clonidine (an α_2-adrenergic agonist) and octreotide (a long-acting somatostatin analog) have been used with some success in persons with rapid transit.[30] Antibiotics are used for those with small bowel bacterial overgrowth secondary to slow transit. As with gastroparesis, strict control of blood glucose is important.

Nephropathies

Diabetic nephropathy is the leading cause of chronic kidney disease, accounting for 40% of new cases.[37] The complication affects people with both type 1 and type 2 diabetes and many of those who have diabetic nephropathy also have some degree of retinopathy.[38] The occurrence of diabetic nephropathy is also associated with increased cardiac risk, and a primary cause of death for those with diabetic kidney disease is cardiovascular disease.[38] The term *diabetic nephropathy* is used to describe the combination of lesions that often occur concurrently in the diabetic kidney. The most common kidney lesions

in people with diabetes are those that affect the glomeruli. Various glomerular changes may occur in people with diabetic nephropathy, including capillary basement membrane thickening, diffuse glomerular sclerosis, and nodular glomerulosclerosis. Changes in the capillary basement membrane take the form of thickening of basement membranes along the length of the glomeruli.[38] Nodular glomerulosclerosis is a form of glomerulosclerosis that involves the development of nodular lesions in the glomerular capillaries of the kidneys, causing impaired blood flow with progressive loss of kidney function and, eventually, renal failure.[38] Nodular glomerulosclerosis is thought to occur only in people with diabetes. Changes in the basement membrane in diffuse glomerulosclerosis allow plasma proteins to escape into the urine, causing proteinuria and the development of hypoproteinemia, edema, and others signs of impaired kidney function.[38]

Not all people with diabetes develop clinically significant nephropathy; for this reason, attention is focusing on risk factors for the development of this complication. Among the suggested risk factors are genetic and familial predisposition, elevated blood pressure, poor glycemic control, smoking, hyperlipidemia, and microalbumuria.[8] Diabetic nephropathy occurs in family clusters, suggesting a familial predisposition, although this does not exclude the possibility of environmental factors shared by siblings. The risk for development of kidney disease is greater among Native Americans, Hispanic Americans (especially Mexican Americans), and African Americans.[8,38]

Kidney enlargement, nephron hypertrophy, and hyperfiltration occur early in the disease, reflecting the increased work performed by the kidneys in reabsorbing excessive amounts of glucose.[38] One of the first manifestations of diabetic nephropathy is an increase in urinary albumin excretion (*i.e.*, microalbuminuria), which is easily assessed by laboratory methods. A spot urine test to detect microalbumin should be done annually for all persons with diabetes. If microalbumin is detected, a 24-hour test of microalbumin should follow for confirmation. Microalbuminuria is defined as a urine protein loss between 30 and 300 mg/day or an albumin-to-creatinine ratio (A/C ratio) between 30 and 300 µg/mg (normal <30 µg/mg) from a spot urine collection.[38] Once kidney disease is established the stage of nephropathy is determined by glomerular filtration rate (GFR).[38] Measures to prevent diabetic nephropathy or its progression in persons with diabetes include achievement of glycemic control; maintenance of blood pressure (<130/80 mm Hg or <120/70 mm Hg in the presence of significant proteinuria); prevention or reduction in the level of proteinuria (using angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or protein restriction in selected patients); treatment of hyperlipidemia; and smoking cessation in people who smoke.[8,38] Smoking increases the risk of chronic kidney disease in persons with and without diabetes. People with type 2 diabetes who smoke have a greater risk of microalbuminuria, and their rate of progression to chronic kidney disease is approximately twice as rapid as in those who do not smoke.[8]

Retinopathies

Diabetes is the leading cause of vision loss and blindness in the United States.[39] Although people with diabetes are at increased risk for development of cataracts and glaucoma, retinopathy is the most common pattern of eye disease. Diabetic retinopathy is estimated to be the most frequent cause of newly diagnosed blindness among Americans between the ages of 20 and 74 years.[40]

Diabetic retinopathy is characterized by abnormal retinal vascular permeability, microaneurysm formation, neovascularization and associated hemorrhage, scarring, and retinal detachment.[39] Retinopathy develops in varying degrees in almost all people with diabetes. Pregnancy, puberty, and cataract surgery can accelerate these changes.[39] Among the suggested risk factors associated with diabetic retinopathy are poor glycemic control, elevated blood pressure, and hyperlipidemia. The strongest case for control of blood glucose comes from the DCCT and UKPDS studies, which demonstrated a reduction in retinopathy with improved glucose control.[31,32]

Because of the risk of retinopathy, it is important that people with diabetes have regular dilated eye examinations. They should have an initial examination for retinopathy shortly after the diagnosis of diabetes is made.[40] The recommendation for follow-up examinations is based on the type of examination that was done and the findings of that examination. Generally, all people with diabetes should have an annual eye exam with more frequent exams for those with persistently poor glucose control or evidence of eye disease.[40]

People with macular edema, moderate to severe nonproliferative retinopathy, or any proliferative retinopathy should receive the care of an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy.[39] Methods used in the treatment of diabetic retinopathy include the destruction and scarring of the proliferative lesions with laser photocoagulation. Photocoagulation is directed to areas of chronic leakage to reduce chronic leakage in people with macular edema.[39]

KEY POINTS

CHRONIC COMPLICATIONS OF DIABETES

- The chronic complications of diabetes result from elevated blood glucose levels and associated impairment of lipid and other metabolic pathways.
- Macrovascular disorders such as coronary heart disease, stroke, and peripheral vascular disease reflect the combined effects of unregulated blood glucose levels, elevated blood pressure, and hyperlipidemia.
- The chronic complications of diabetes are best prevented by measures aimed at tight control of blood glucose levels, maintenance of normal lipid levels, and control of hypertension.

Macrovascular Complications

DM is a major risk factor for coronary artery disease, cerebrovascular disease, and peripheral vascular disease. The prevalence of these macrovascular complications is increased twofold to fourfold in people with diabetes.[41] Approximately 50% to 75% of all people with type 2 diabetes die of a macrovascular problem.[41]

Multiple risk factors for macrovascular disease, including obesity, hypertension, hyperglycemia, hyperinsulinemia, hyperlipidemia, altered platelet function, endothelial dysfunction, systemic inflammation (as evidenced by increased CRP), and elevated fibrinogen levels, are frequently found in people with diabetes.[41] There appear to be differences between type 1 and type 2 diabetes in terms of duration of disease and the development of macrovascular disease. People with type 1 diabetes are at an increased risk of cardiovascular events but may not have other classic risk factors, such as obesity. In people with type 2 diabetes, macrovascular disease may be present at the time of diagnosis. Increased risk for cardiovascular events in this group may be related to the components of metabolic syndrome.[41] Aggressive management of cardiovascular risk factors should include smoking cessation, hypertension, lipid lowering, diabetes control, and antiplatelet agents (aspirin or clopidogrel) if not contraindicated.[15,41] Lifestyle changes, which decrease cardiovascular risk factors should be strongly encouraged and supported by the health care team. Diet, exercise, weight loss, and glycemic control can help reduce the incidence of cardiovascular events.

Diabetic Foot Ulcers

Foot problems are common among people with diabetes and may become severe enough to cause ulceration, infection, and, eventually, the need for amputation. In people with diabetes, lesions of the feet represent the effects of neuropathy and vascular insufficiency. Approximately 60% to 70% of people with diabetic foot ulcers have neuropathy without vascular disease, 15% to 20% have vascular disease, and 15% to 20% have neuropathy and vascular disease.[35]

Distal symmetric neuropathy is a major risk factor for foot ulcers. People with sensory neuropathies have impaired pain sensation and are often unaware of the constant trauma to the feet caused by poorly fitting shoes, improper weight bearing, hard objects or pebbles in the shoes, or infections such as athlete's foot.[35] Neuropathy prevents people from detecting pain; thus injuries and infections often go undetected. Motor neuropathy with weakness of the intrinsic muscles of the foot may result in foot deformities, which lead to focal areas of high pressure.[42] When the abnormal focus of pressure is coupled with loss of sensation, a foot ulcer can occur. Common sites of trauma are the back of the heel, the plantar metatarsal area, or the great toe, where weight is borne during walking (Fig. 50.11).

All persons with diabetes should receive a full foot examination at least once a year. This examination should include assessment of protective sensation, foot structure and biomechanics, vascular status, and skin integrity.[34] Evaluation of neurologic function should include a somatosensory test using either the Semmes-Weinstein monofilament or vibratory sensation.[8] The Semmes-Weinstein monofilament is a simple, inexpensive device for testing sensory status (Fig. 50.12). The monofilament is held in the hand or attached to a handle at one end. When the unattached or unsupported end of the monofilament is pressed against the skin until it buckles or bends slightly, it delivers 10 g of pressure at the point of contact.[35] The test consists of having the person being tested report the sensation when touched by the monofilament.

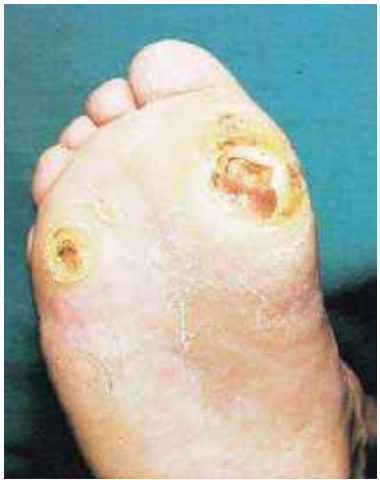


FIGURE 50.11 • Neuropathic ulcers occur on pressure points in areas with diminished sensation in diabetic polyneuropathy. Pain is absent (and therefore the ulcer may go unnoticed until it enlarges). (From Jensen S. (2011). *Nursing health assessment: A best practice approach* (p. 557). Philadelphia, PA: Lippincott Williams & Wilkins.)

Because of the constant risk of foot problems, prevention of injury or early detection is critical. It is important that people with diabetes wear shoes that have been fitted correctly

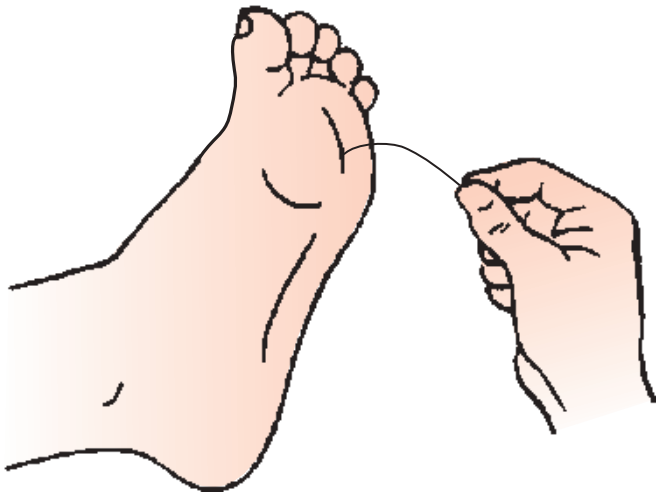


FIGURE 50.12 • Use of a monofilament in testing for impaired sensation in the foot of a person with diabetes.

and inspect their feet daily, looking for blisters, open sores, and fungal infection (*e.g.*, athlete's foot) between the toes. If their eyesight is poor, a family member should do this for them. Education supporting prompt medical attention for skin lesions is needed to prevent serious complications. Smoking should be avoided because it causes vasoconstriction and contributes to vascular disease. Because cold produces vasoconstriction, appropriate foot coverings should be used to keep the feet warm and dry. Toenails should be cut straight across to prevent ingrown toenails. The toenails are often thickened and deformed, requiring the services of a podiatrist. Self-treatment of foot problems in this population, such as difficult toe nails, calluses, and other issues, should be strongly discouraged.

Advances in the field of chronic wound care have increased treatment options for this population. Ulcers that are resistant to standard therapy may respond to application of growth factors. Growth factors provide a means by which cells communicate with each other and can have profound effects on cell proliferation, migration, and extracellular matrix synthesis. Use of hyperbaric oxygen therapy, wound cares specialty services, and minimally invasive surgeries provide options for chronic wounds, but add to the financial burden of diabetes on health care resources.[43]

Infections

Although not specifically an acute or a chronic complication, infections are a common concern of people with diabetes. Certain types of infections occur with increased frequency in people with diabetes: soft tissue infections of the extremities, osteomyelitis, urinary tract infections and pyelonephritis, candidal infections of the skin and mucous surfaces, dental caries and periodontal disease.[9] Suboptimal response to infection in a person with diabetes is caused by the presence of chronic complications, such as vascular disease and neuropathies, and by the presence of hyperglycemia and altered neutrophil function.[26] Sensory deficits may cause a person with diabetes to ignore minor trauma and infection, and vascular disease may impair circulation and delivery of blood cells and other substances needed to produce an adequate inflammatory response and effect healing. Hyperglycemia and glycosuria may influence the growth of microorganisms and increase the severity of the infection.[9] In acute illness, increased efforts to control blood sugars for surgical patients and medical conditions cite an impact on infections.[44]

Once an individual is diagnosed with diabetes, regardless of the type, they should work with a health care team to achieve optimal glycemic control and have regular screenings for diabetes complications. These recommendations include A1C testing two to four times a year depending on control, annual dilated eye exam, foot exam, lipid profile, microalbumin, serum creatinine, blood pressure, and weight.[8] Prevention and delay of complications is possible with adherence to lifestyle interventions that support health such as good nutrition, exercise, and preventative care.

IN SUMMARY

DM is a disorder of carbohydrate, protein, and fat metabolism resulting from an imbalance between insulin availability and insulin need. The disease can be classified as type 1 diabetes, in which there is destruction of beta cells and an absolute insulin deficiency, or type 2 diabetes, in which there is a lack of insulin availability or effectiveness. Type 1 diabetes can be further subdivided into type 1A immune-mediated diabetes, which is thought to be caused by autoimmune mechanisms, and type 1B idiopathic diabetes, for which the cause is unknown. GDM develops during pregnancy, and although glucose tolerance often returns to normal after childbirth, it indicates an increased risk for the development of diabetes. The metabolic syndrome represents a constellation of metabolic abnormalities characterized by obesity, insulin resistance, high triglyceride levels and low HDL levels, hypertension, cardiovascular disease, insulin resistance, and increased risk for development of type 2 diabetes.

The most commonly identified symptoms of type 1 diabetes are polyuria, polydipsia, polyphagia, and weight loss despite normal or increased appetite. Although persons with type 2 diabetes may present with one or more of these symptoms, they are often asymptomatic initially. The diagnosis of DM is based on clinical signs of the disease, fasting blood glucose levels, random plasma glucose measurements, and results of the glucose tolerance test. Glycosylation involves the irreversible attachment of glucose to the hemoglobin molecule; the measurement of A1C provides an index of blood glucose levels over several months. Self-monitoring provides a means of maintaining near-normal blood glucose levels through frequent testing of blood glucose and adjustment of insulin dosage.

Dietary management focuses on maintaining a well-balanced diet, controlling calories to achieve and maintain an optimum weight, and regulating the distribution of carbohydrates, proteins, and fats. Two types of antidiabetic agents are used in the management of diabetes: injectable agents and oral diabetic drugs. Injectable agents traditionally have included the family of insulin agents but now include newer agents, such as amylin and GLP-1 analogs. Oral diabetic drugs include a variety of options. Type 1 diabetes (always), and type 2 (sometimes), requires treatment with injectable insulin. Oral antidiabetic drugs include the insulin secretagogues, biguanides, α-glucosidase inhibitors, TZDs, and DPP-4 enzyme inhibitors. These drugs require a functioning pancreas and may be used in the treatment of type 2 diabetes.

The metabolic disturbances associated with diabetes affect almost every body system. The acute complications of diabetes include DKA, hyperglycemic hyperosmolar state, and hypoglycemia in people with insulin-treated

CHAPTER 21

Urinary System Disorders

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, the student is expected to:

1. Compare the etiology, pathophysiology, and manifestations of cystitis and pyelonephritis.
2. Explain the development of acute poststreptococcal glomerulonephritis, its signs and symptoms, including laboratory tests and possible complications.
3. Describe the etiology and significant manifestations of nephrotic syndrome.
4. Explain the common signs and symptoms of urinary tract obstruction.
5. List common causes of urinary calculi.
6. Explain how hydronephrosis develops and its effects on the kidney.
7. Describe the incidence and early signs of adenocarcinoma of the kidney, bladder cancer, and Wilms' tumor.
8. Explain how nephrosclerosis affects: (a) the kidney, and (b) systemic blood pressure.
9. Describe the etiology, usual age at onset, manifestations, and outcome of adult polycystic disease.
10. Compare acute and chronic renal failure with regard to common causes, pathophysiology, signs and symptoms, and possible complications.
11. Explain how peritoneal dialysis or hemodialysis substitutes for a nonfunctioning kidney, including limitations of the therapy.

KEY TERMS

anasarca
anuria
azotemia
calculi
dialysate
dysuria
frequency
glucosuria
hematuria
nocturia
oliguria
osteodystrophy
polyuria
proteinuria
pyuria
renal colic
retroperitoneally
ultrafiltration
urgency

REVIEW OF THE URINARY SYSTEM

The purpose of the urinary system is to:

- Remove metabolic wastes (nitrogenous and acidic)
- Remove hormones, drugs, and other foreign material from the body
- Regulate water, electrolytes, and acid-base balance in the body
- Secrete erythropoietin
- Activate vitamin D
- Regulate blood pressure through the renin-angiotensin-aldosterone system

THINK ABOUT 21-1

a. Explain the function of erythropoietin and the effects of a deficit of this hormone.
b. Explain the function vitamin D and the possible effects of a deficit of this vitamin.

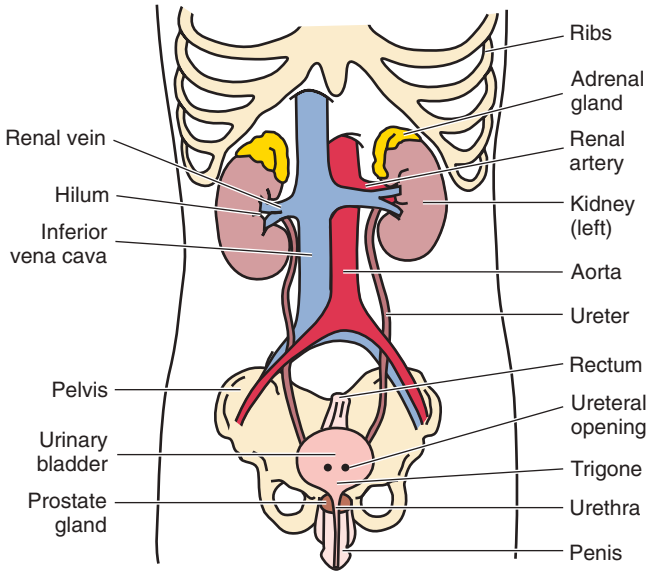


FIGURE 21-1 Gross anatomy of the urinary system (male).

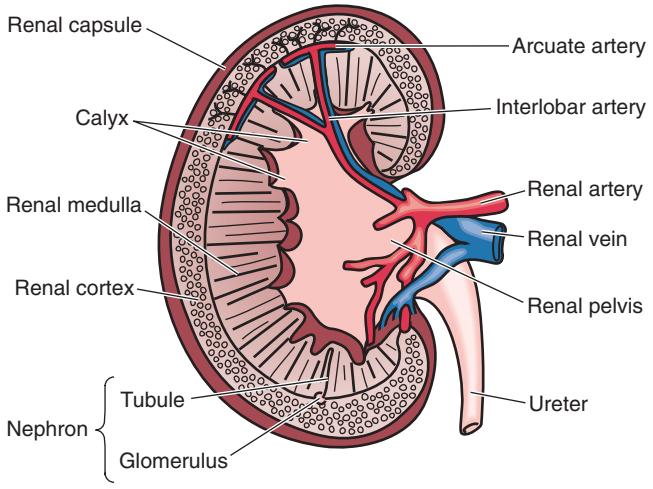


FIGURE 21-2 Anatomy of the kidney.

The two kidneys are bean-shaped structures, each the size of a fist, located behind the peritoneum (that is, **retroperitoneally**) on the posterior abdominal wall. The kidneys are covered by a fibrous *capsule* and are embedded in fat, with the superior portion also protected by the lower ribs (Fig. 21-1).

Inside each kidney is the *cortex,* or outer layer, in which the majority of the glomeruli are located, and the *medulla,* or inner section of tissue, which consists primarily of the tubules and collecting ducts. Inside the medulla lie the *renal pelvis* and calyces, through which urine flows into the ureter (Fig. 21-2).

Each kidney consists of over a million *nephrons,* the functional units of the kidney (Fig. 21-3). The renal corpuscle consists of Bowman's capsule (glomerular capsule), which is the blind end of the proximal convoluted tubule. This capsule surrounds a network of capillaries, called the glomerulus or glomerular capillaries. These form the filtration unit for the blood.

During *filtration,* a large volume of fluid, including wastes, nutrients, electrolytes, and other dissolved substances, passes from the blood into the tubule. Cells and protein remain in the blood (Table 21-1). When the filtration pressure increases, more filtrate forms, and more urine is produced. The filtrate flows into the *tubules.* The tubule consists of three parts, the proximal convoluted tubule, the loop of Henle, and the distal convoluted

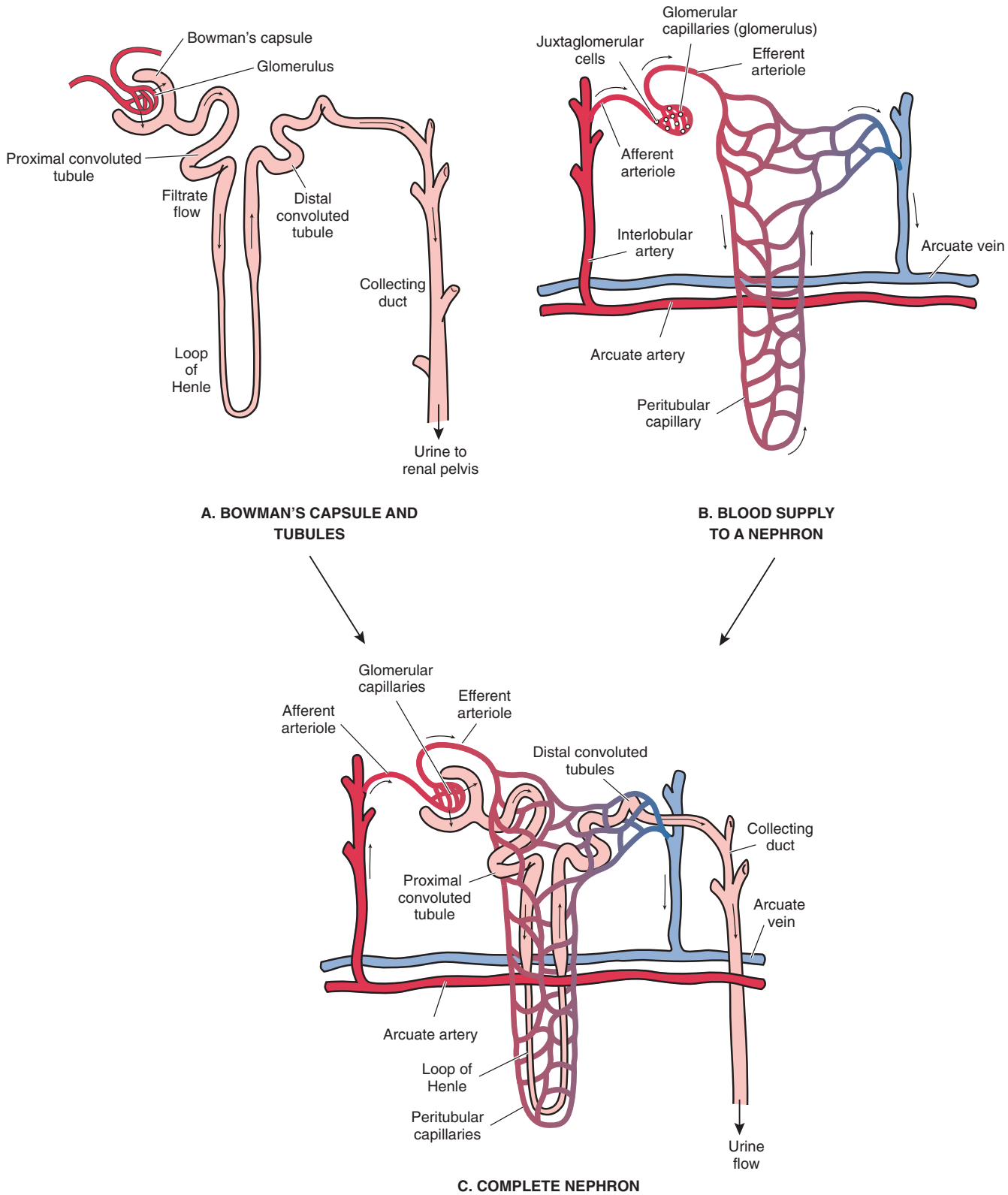


FIGURE 21-3 The nephron. **A**, Glomerulus and tubules. **B**, Blood supply to the nephron. **C**, Complete nephron.

staltic movements assist its flow to the urinary bladder. The renal pelvis, calyces, ureters, and bladder are lined with transitional epithelium that is not permeable to water and can resist the irritation of constant contact with urine.

The *bladder* is composed of smooth muscle that falls in rugae, or folds, to form an expandable sac. It is located retroperitoneally in the pelvic cavity. The bladder has openings for the two ureters to bring urine in and an outlet for the urethra through which urine flows out of the body. The triangular section outlined by these three openings is called the trigone (see Fig. 21-1).

The female *urethra* is 3 to 4 cm long. It is relatively short and wide and opens onto the perineum anterior to the vagina and anus. The proximity of the urethra to these two sources promotes infection of the bladder in women.

The male urethra is about 20 cm long and passes through the penis. At the base of the male bladder is the prostate gland, which plays a role in semen production and frequently is hypertrophied in older men, obstructing urine flow (see Chapter 28 for reproductive disorders). During orgasm in the male, a sphincter closes off the flow of urine and semen is ejaculated through the urethra.

The mucosa lining the urinary tract is continuous through the urethra, bladder, and ureter to the pelvis of the kidney. Organisms can easily enter the system through the urethra, and this continuous mucosa facilitates the spread of infection through the urinary tract (an ascending infection).

Micturition (urination, voiding) occurs when a reflex is stimulated by increased pressure as the bladder distends. The reflex is transmitted by parasympathetic nerves extending to the sacral spinal cord. If the time is appropriate, under voluntary control, the external and internal sphincters of the bladder and the pelvic diaphragm relax while the bladder muscle contracts, emptying the bladder.

CHALLENGE 21-1

Predict four ways in which urinary system function can become impaired. Explain how a specific pathologic process such as inflammation would affect the function of the part.

INCONTINENCE AND RETENTION

Incontinence, or the loss of voluntary control of the bladder, has many causes. Young children must learn voluntary control as the nervous system matures. *Enuresis* defines involuntary urination by a child after age 4 to 5, when bladder control can be expected. Most children have nocturnal enuresis only. The majority of cases appear to be related to factors such as a developmental delay, sleep pattern, or psychosocial aspects rather than to a physical defect. *Stress incontinence* occurs when increased intra-abdominal pressure forces urine through the sphincter. This can occur with coughing, lifting, or laughing, but occurs more frequently in women after the urogenital diaphragm has become weakened by multiple pregnancies or age. *Overflow incontinence* results from an incompetent bladder sphincter. In the elderly, a weakened detrusor muscle may prevent complete emptying of the bladder, leading to frequency and incontinence. Spinal cord injuries or brain damage frequently cause a neurogenic bladder, which may be spastic or flaccid, due to interference with central nervous system (CNS) and autonomic nervous system control of the bladder emptying.

Retention is an inability to empty the bladder. It may be accompanied by overflow incontinence. Note that a spinal cord injury at the sacral level blocks the micturition reflex, resulting in retention of urine or failure to void. Retention also may occur after anesthesia, either general or spinal. Inability to control urine flow may be managed by wearing pads or briefs that contain the urine.

A *catheter* is a tube inserted in the urethra that drains urine from the bladder to a collecting bag outside the body. Catheters are common sources of infection in the urinary tract because they are irritating to the tissue and, when inserted, may be a means of introducing bacteria directly into the bladder if sterile technique is not used. Catheters prevent kidney damage due to backup of urine, collect urine, and prevent skin breakdown in the incontinent client.

THINK ABOUT 21-6

Locate the urinary bladder relative to the uterus and rectum in a woman. Briefly explain two possible implications of this location.

DIAGNOSTIC TESTS

URINALYSIS

The constituents and characteristics of urine may vary with dietary intake, drugs, and the care with which a specimen is handled. Urine normally is clear and straw-colored and has a mild odor. Urine pH is in the range of 4.5 to 8.0. The following lists offer general guidelines to common abnormalities noted in freshly voided specimens. An "old" specimen will not provide accurate information. See the inside front cover of this book for normal values.

Appearance

- Cloudy—may indicate the presence of large amounts of protein, blood cells, or bacteria and pus
- Dark color—may indicate **hematuria** (blood), excessive bilirubin content, or highly concentrated urine
- Unpleasant or unusual odor—may indicate infection or result from certain dietary components or medications

Abnormal Constituents (Present in Significant Quantities)

- Blood (hematuria)—small (*microscopic*) amounts of blood are often associated with infection, inflammation, or tumors in the urinary tract; large numbers of red blood cells (*gross* hematuria) indicate increased glomerular permeability or hemorrhage in the tract
- Protein (**proteinuria,** albuminuria)—indicates the leakage of albumin or mixed plasma proteins into the filtrate owing to inflammation and increased glomerular permeability
- Bacteria (bacteriuria) and pus (**pyuria**)—indicate infection in the urinary tract (Fig. 21-6*A*)
- Urinary *casts* (microscopic-sized molds of the tubules, consisting of one or more cells, bacteria, protein, and so on)—indicate inflammation of the kidney tubules (see Fig. 21-6*B*)
- Specific gravity indicates the ability of the tubules to concentrate the urine; a very low specific gravity (dilute urine) usually is related to renal failure (assuming normal hydration)
- Glucose and ketones (ketoacids) are found in the urine when diabetes mellitus is not well controlled (see Chapter 25)

THINK ABOUT 21-7

a. Explain the presence of the normal constituents of urine.
b. Explain why hematuria and proteinuria reflect a glomerular problem rather than a tubular problem in the kidney.

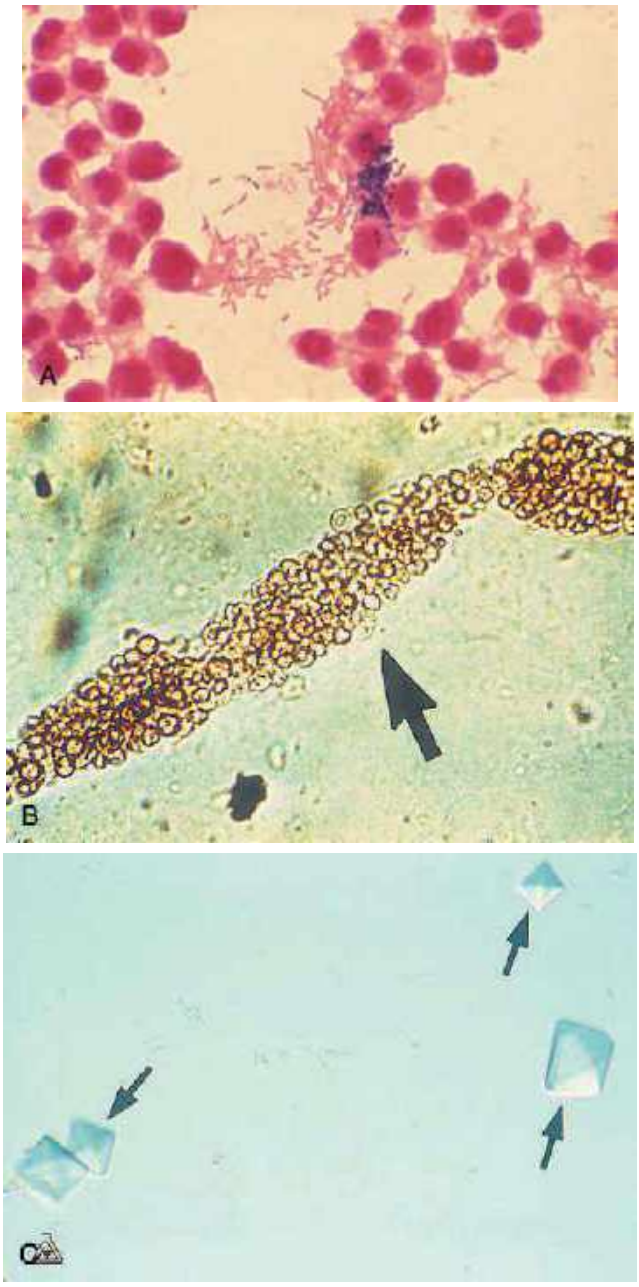


FIGURE 21-6 **A**, Urinalysis—smear shows infection with heavy purulence and presence of gram-negative and gram-positive organisms (*E. coli* and *Enterococcus faecalis*) (density of microbes 10^5/mL urine). **B**, Urinalysis—red blood cell cast. **C**, Urinalysis-—calcium oxalate crystals in the urine. (***A***, *From Mahon CR, Manuselis G:* Textbook of Diagnostic Microbiology, *2nd ed. Philadelphia, WB Saunders, 2000.* ***B*** *and* ***C*** *from Stepp CA, Woods M:* Laboratory Procedures for Medical Office Personnel. *Philadelphia, WB Saunders, 1998.)*

BLOOD TESTS

Like most other diseases, urinary tract disorders produce abnormalities that can be detected by various blood tests. Some of the more commonly used tests and implications are described here.

- Elevated serum urea (blood urea nitrogen [BUN]) and serum creatinine—indicate failure to excrete nitrogen wastes (resulting from protein metabolism) due to decreased GFR
- Metabolic acidosis (decreased serum pH and decreased serum bicarbonate)—indicates decreased GFR and failure of the tubules to control acid-base balance (see Chapter 6)
- Anemia (low hemoglobin level)—indicates decreased erythropoietin secretion and/or bone marrow depression, due to accumulated wastes

THINK ABOUT 21-11

List the signs and symptoms of pyelonephritis that indicate that *infection* is present and mark those indicating that *kidney involvement* (local or systemic) exists.

INFLAMMATORY DISORDERS

Glomerulonephritis (Acute Poststreptococcal Glomerulonephritis)

There are many forms of glomerulonephritis. A representative form of glomerular or nephritic disease is acute poststreptococcal glomerulonephritis (APSGN), which follows streptococcal infection with certain strains of group A beta-hemolytic *Streptococcus*. These infections usually originate as upper respiratory infections, middle ear infections, or "strep throat." Certain strains of *Staphylococcus* are occasionally responsible for initiating the immune disorder in the kidney.

Acute glomerulonephritis develops 10 days to 2 weeks after the antecedent infection. APSGN affects primarily children between the ages of 3 and 7 years, especially boys.

Pathophysiology

The antistreptococcal antibodies, formed as usual from the earlier streptococcal infection, create an antigen-antibody complex (type III hypersensitivity reaction) that lodges in the glomerular capillaries, activates the complement system to cause an inflammatory response in the glomeruli of both kidneys (Fig. 21-9). (See Chapter 3 for a review of the immune response.) This leads to increased capillary permeability and cell proliferation (Fig. 21-10) and results in leakage of some protein and large numbers of erythrocytes into the filtrate. The specific mechanisms of damage are not totally clear, but immunoglobulin G and C3 (complement) are present in glomerular tissue and serum C3 is reduced.

When the inflammatory response is severe, the congestion and cell proliferation interfere with filtration in the kidney, causing decreased GFR and retention of

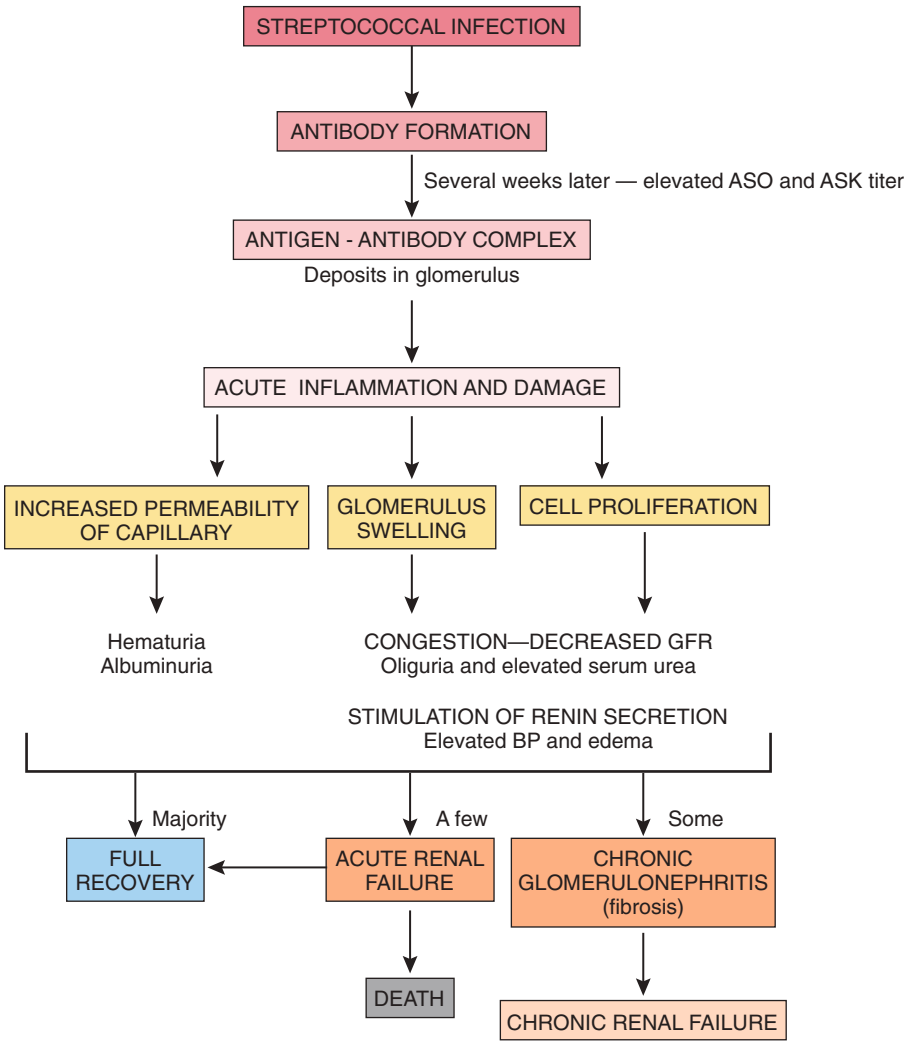


FIGURE 21-9 Development and course of poststreptococcal glomerulonephritis.

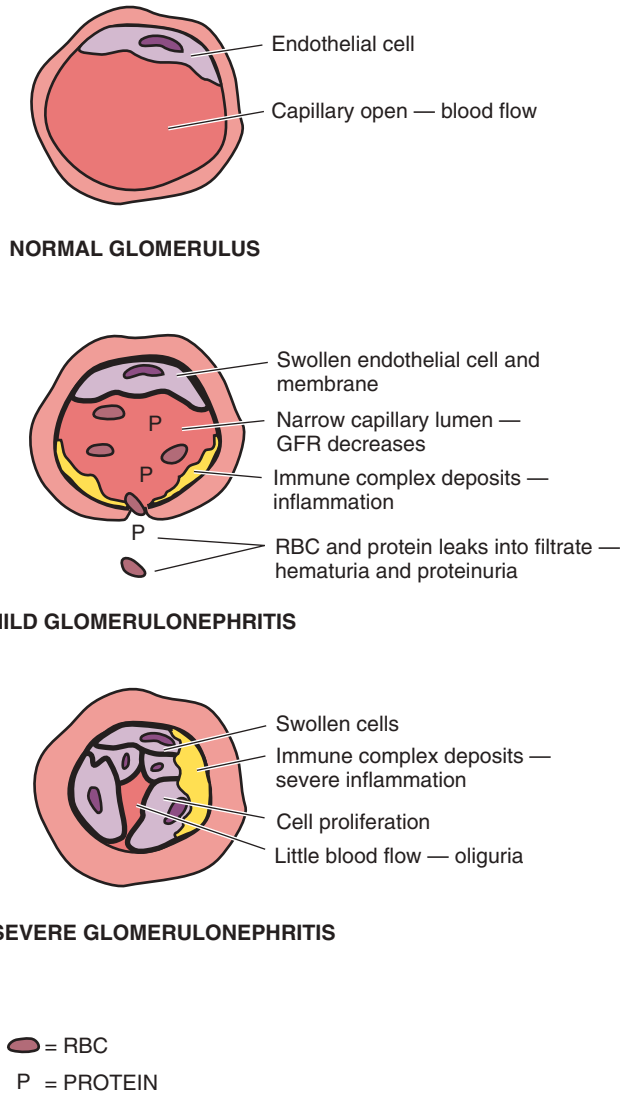


FIGURE 21-10 Schematic representation of changes occurring in the nephron with acute poststreptococcal glomerulonephritis.

fluid and wastes. Acute renal failure is possible if blood flow is sufficiently impaired. The decreased blood flow in the kidney is likely to trigger increased renin secretion, which leads to elevated blood pressure and edema (see Fig. 21-13). Severe prolonged inflammation causes scarring of the kidneys.

Signs and symptoms

- The urine becomes dark and cloudy ("smoky" or "coffee-colored") because of the protein and red blood cells that have leaked into it.
- Facial and periorbital edema occur initially, followed by generalized edema as the colloid osmotic pressure of the blood drops and sodium and water are retained.
- Blood pressure is elevated owing to increased renin secretion and decreased GFR.
- Flank or back pain develops as the kidney tissue swells and stretches the capsule.
- General signs of inflammation are present, including malaise, fatigue, headache, anorexia, and nausea.
- Urine output decreases (oliguria) as GFR declines.

Diagnostic tests

- *Blood tests* show elevated serum urea and creatinine as GFR decreases.
- Blood levels of Anti DNase B, streptococcal antibodies, ASO, and ASK are elevated.
- Complement level is decreased. It is probably a causative factor in the inflammatory damage that occurs in the kidney.
- Metabolic acidosis, with decreased serum bicarbonate and low serum pH, is present.
- *Urinalysis* confirms the presence of proteinuria, gross hematuria, and erythrocyte casts (see Fig. 21-6*B*).

Treatment

Sodium restrictions may apply, and in severe cases, protein and fluid intake is decreased. Drug treatment includes glucocorticoids to reduce the inflammation, and antihypertensives to reduce high blood pressure.

In most cases, recovery takes place with minimum residual damage, although it is important to prevent future exposure to streptococcal infection and recurrent inflammation due to another hypersensitivity reaction. In children, the edema usually recedes in 5 to 10 days, and hypertension decreases in 2 to 3 weeks. Proteinuria and hematuria improve but often persist for some time. Prophylactic antibiotics may be needed. Post-recovery testing is recommended to ensure that chronic inflammation is not present.

Some cases, particularly in adults, are not easily resolved. Acute renal failure occurs in approximately 2% of cases. Chronic glomerulonephritis develops in about 10%, which gradually destroys the kidneys through end-stage renal disease or uremia.

THINK ABOUT 21-12

a. Explain the development of inflammation in the kidney with APSGN.
b. Describe the signs of APSGN related to: (1) increased glomerular permeability, and (2) decreased glomerular filtration rate.

Nephrotic Syndrome (Nephrosis)

The nephrotic syndrome is secondary to a number of renal diseases as well as to a variety of systemic disorders (e.g., systemic lupus erythematosus [SLE], exposure to toxins or drugs). However, lipoid nephrosis, also known as minimal change disease, is a primary disease in young children ages 2 to 6 years.

Pathophysiology

The pathogenesis is not well established, but the following sequence develops.

1. There is an abnormality in the glomerular capillaries and increased permeability that allows large amounts of plasma protein, primarily albumin, to escape into the filtrate.
2. This results in marked hypoalbuminemia with decreased plasma osmotic pressure and subsequent generalized edema.
3. Blood pressure may remain low or normal in many cases because of hypovolemia or it may be elevated depending on angiotensin II levels.
4. The decreased blood volume also increases aldosterone secretion, leading to more severe edema.
5. The other significant components of nephrotic syndrome are the high levels of cholesterol in the blood and lipoprotein in the urine. The cause of the hyperlipidemia and lipiduria is not totally clear, although it appears to be related to the response of the liver to heavy protein loss.

Signs and symptoms

Urinalysis indicates marked proteinuria, lipiduria and casts (fatty, epithelial, and hyaline). Cells may be present with certain primary diseases. Urine is often frothy.

The significant sign of nephrosis is the massive edema (**anasarca**) associated with weight gain and pallor. This excessive fluid throughout all tissues impairs appetite (ascites), breathing (pleural effusion), and activity (swollen legs and feet). Skin breakdown and infection may develop because arterial flow and capillary exchange are impaired.

THINK ABOUT 21-13

Compare the characteristics of the urine in a child with pyelonephritis, APSGN, or nephrotic syndrome.

Treatment

Glucocorticoids such as prednisone are prescribed to reduce the inflammation in the kidney. ACE inhibitor drugs, such as ramipril, may decrease protein loss in the urine. Antihypertensive and antilipemic therapy may be required in some individuals. Nephrotic syndrome tends to recur and requires frequent monitoring and continued treatment. Recurrences may be treated with cytotoxic therapies such as cyclophosphamide. When administered long term, glucocorticoids have significant negative effects on a child's growth (see Chapter 2 for long-term effects of therapy). Sodium intake may be restricted, but protein intake is usually increased.

RESEARCH 21-1

Research continues to clarify the pathophysiology and etiology of acute glomerulonephritis and nephrotic syndrome. Compile three questions you would ask regarding the pathophysiology, etiology, or specific rationale for a particular manifestation.

URINARY TRACT OBSTRUCTIONS

In older men, the urinary tract is frequently obstructed by benign prostatic hypertrophy or prostatic cancer. These topics are discussed in Chapter 28.

Renal calculi are a common cause of obstruction in men and women.

UROLITHIASIS (CALCULI, OR KIDNEY STONES)

Kidney stones are a common problem and frequently recur if the underlying cause is not treated.

Pathophysiology

Calculi can develop anywhere in the urinary tract. Stones may be small or very large (e.g., *staghorn* calculus, a very large stone that forms in the renal pelvis and calyces in the shape of a deer's antlers).

Calculi tend to form when there are excessive amounts of relatively insoluble salts in the filtrate, or when insufficient fluid intake creates a highly concentrated filtrate. Once any solid material or debris forms, deposits continue to build up on this nidus, or focus, and eventually form a large mass. Cell debris from infection may also form a nidus. Immobility may result in calculi in the kidney because of stasis of urine resulting in chemical changes in the urine. Increasing fluid intake (at least eight glasses of water per day) can assist in removing small stones quickly from the urinary tract.

Stones usually cause manifestations only when they obstruct the flow of urine (e.g., in the ureter). Calculi may lead to infection because they cause stasis of urine in the area and also irritate the tissues. This may be an early indication of calculi formation.

When located in the kidney or ureter, calculi may cause the development of *hydronephrosis,* with dilation of calyces and atrophy of renal tissue related to the back pressure of urine behind the obstructing stone (Fig. 21-11).

Etiology

Approximately 75% of calculi are composed of calcium salts, the remainder consisting primarily of uric acid (a breakdown product of purine nucleotides) or urates, struvite (magnesium ammonium phosphate), or cystine (rare), depending on the predisposing factor. Calculi should be examined and urinalysis completed to determine the content of the stones and the predisposing factors.

Calcium stones (phosphate, oxalate, or carbonate) form when calcium levels in the urine are high owing to hypercalcemia, perhaps due to a parathyroid tumor or other metabolic disorder (see Fig. 21-6*C*). The solubility of calcium salts and uric acid also varies with the *pH* of the urine. Calcium stones form readily when the urine is highly alkaline. Inadequate fluid intake is a major factor in calculus formation. Calcium oxalate

stones may develop in people following vegetarian diets high in oxalate that lead to increased levels of oxalate in the urine.

Uric acid stones develop with hyperuricemia (due to gout, high purine diets, or cancer chemotherapy), especially when the urine is acidic. Infection may cause stones consisting of mixed inorganic salts, because in such cases the urine pH is alkaline and debris from the infection may act as a focus for the deposition of crystals.

THINK ABOUT 21-14

Explain how decreased fluid intake or dehydration predisposes to calculi in the urinary tract.

Signs and symptoms

Stones in the kidney or bladder are frequently asymptomatic, unless frequent infections lead to investigation. Sometimes flank pain occurs because of distention of the renal capsule.

Obstruction of the ureter causes an attack of "**renal colic**," consisting of intense spasms of pain in the flank area radiating into the groin that last until the stone passes or is removed. This pain is caused by vigorous contractions of the ureter in an effort to force the stone out. The severe pain may be accompanied by nausea and vomiting, cool moist skin, and rapid pulse. Radiologic examination confirms the location of the calculi.

Treatment

Small stones can be passed eventually, the urine strained to catch stones for analysis. Newer methods of fragmentation of larger stones, such as extracorporeal shock-wave lithotripsy (ESWL) and laser lithotripsy, have been quite successful and have decreased the need for invasive surgery. In some cases, drugs may be used to partially dissolve the stones.

Prevention of recurrence related to specific risk factors is of primary importance. Treatment of the underlying condition, adjustment of urine pH by ingestion of additional acidic or alkaline substances, and increased fluid intake all minimize the risk of recurrence.

HYDRONEPHROSIS

This occurs as a secondary problem, a complication of calculi, but also of tumors, scar tissue in the kidney or ureter, and untreated prostatic enlargement. Developmental defects are common in the urinary tract and may cause obstruction by kinking or stenosis of a ureter. Obstructive uropathy can be diagnosed by ultrasonography in the fetus, allowing for immediate or neonatal corrective surgery, thus preventing major kidney damage.

Urine is continually forming. Any prolonged interference with urine outflow through the system results in back pressure and a dilated area filled with urine in the ureter or kidney (see Fig. 21-11*B*). In the kidney, continued buildup of urine, particularly over a prolonged period of time, causes necrosis of the tissue

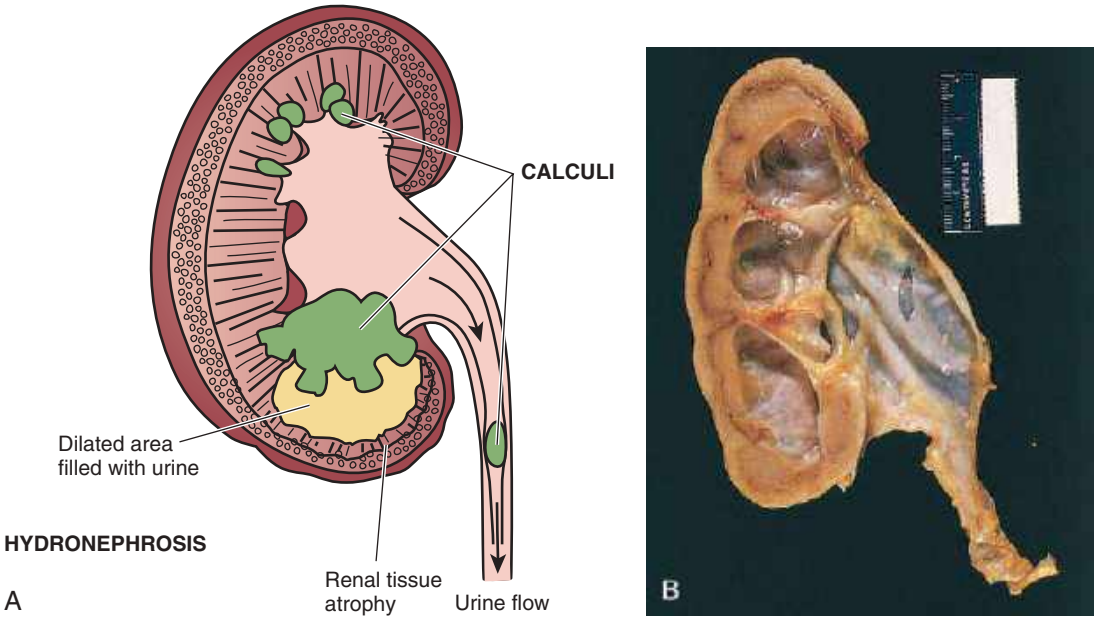


FIGURE 21-11 **A**, Renal calculi and hydronephrosis. **B**, Hydronephrosis with dilation of the renal pelvis and calyces and atrophy of renal tissue. *(From Kumar V, Abbas AK, Fausto M:* Robbins and Cotran Pathologic Basis of Disease, *7th ed. Philadelphia, WB Saunders, 2005.)*

because of direct pressure and compression of the blood vessels. Hydronephrosis is frequently asymptomatic unless mild flank pain occurs as the renal capsule is distended, or unless infection develops. It can be diagnosed with ultrasonography, radionucleotide imaging, CT scan or IVP. If the cause is not removed, bilateral hydronephrosis could lead to chronic renal failure.

TUMORS

Benign tumors are rare in the urinary tract. Malignant tumors occur primarily after age 50 years, in males by a ratio of 3:2. Smoking is a major predisposing factor.

Renal Cell Carcinoma

Renal cell carcinoma (adenocarcinoma of the kidney) is a primary tumor arising from the tubule epithelium, more often in the renal cortex (Fig. 21-12). Approximately 54,000 people in the United States were diagnosed with this cancer in 2008. It tends to be asymptomatic in the early stage and often has metastasized to liver, lungs, bone, or CNS at the time of diagnosis. This cancer occurs more frequently in men and smokers.

The initial sign is usually painless hematuria, either gross or microscopic. Other manifestations include dull, aching flank pain; a palpable mass; unexplained weight loss; and anemia or erythrocytosis (depending on the tumor's effects on erythropoietin secretion). Paraneoplastic syndromes such as hypercalcemia (increased parathyroid hormone) or Cushing's syndrome (increased adrenocorticotropic hormone) are common.

This tumor tends to be silent; therefore, diagnosis is made in one third of cases after metastasis to lungs, liver, or bone has occurred. Removal of the kidney (nephrectomy) is the treatment because the tumor is usually unresponsive to radiation or chemotherapy. The 5-year survival rate varies from 96% in Stage I to 23% in Stage IV; newer treatment measures and diagnostic technology may result in higher survival rates.

Bladder Cancer

Malignant tumors of the bladder commonly arise from the transitional epithelium lining the bladder in the trigone area. This cancer often develops as multiple tumors and tends to recur. It is diagnosed by urine cytology (malignant cells in the urine) and biopsy. The tumor is invasive through the wall to adjacent structures, and it metastasizes through the blood to pelvic lymph nodes, liver, and bone. Staging categories range from an in situ tumor through the degree of bladder wall invasion to metastasis. The early sign is hematuria, gross or microscopic. Dysuria or frequency may develop and infection is common.

Bladder cancer has a high incidence in individuals working with chemicals in laboratories or industry, particularly with dyes, rubber, and aluminum. More than 50% of patients are cigarette smokers. Other predisposing factors are recurrent infection and heavy intake of analgesics.

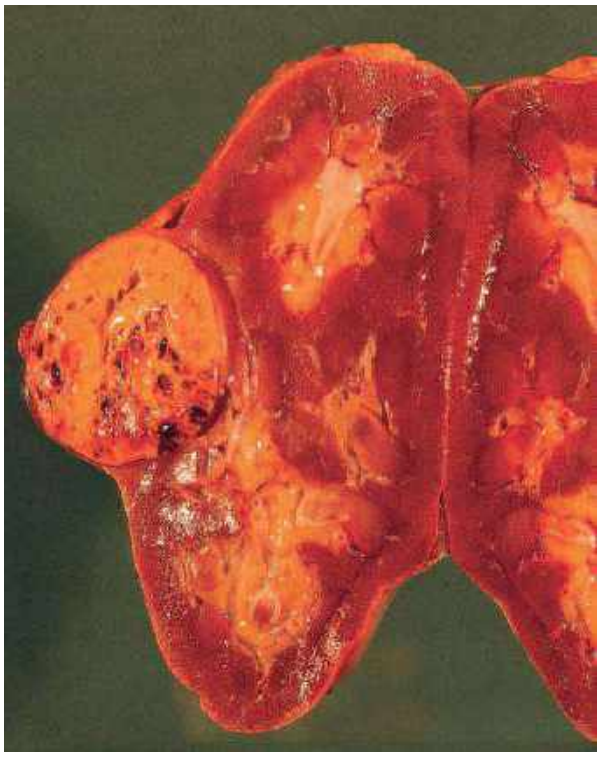


FIGURE 21-12 Renal cell carcinoma. A well-circumscribed spherical tumor is bulging through the cortical surface. Areas of hemorrhage and cysts can be seen in the tumor. *(From Cooke RA, Stewart B:* Colour Atlas of Anatomical Pathology, *3rd ed. Sydney, Churchill Livingstone, 2004.)*

Treatment includes surgical resection of the tumor in 90% of cases, chemotherapy, and radiation. Urinary diversion (e.g., ileal loop, the creation of an alternate internal or external urine collecting unit using part of the ileum) may be required following surgery. Photoradiation (a combination of drug and laser treatment) has been successful in some early cases. Instillation of BCG, bacillus Calmette-Guérin vaccine (a biologic response modifier intended to strengthen the immune response), into the bladder after resection has reduced recurrences of superficial tumors (see Chapter 5). Continued monitoring is necessary to detect recurrences in an early stage. Five-year survival rates vary from 85% in Stage I to 16% in Stage IV.

VASCULAR DISORDERS

NEPHROSCLEROSIS

Pathophysiology

Nephrosclerosis involves vascular changes, similar to those of arteriosclerosis, in the kidney. Some vascular changes occur normally with aging, but these excessive

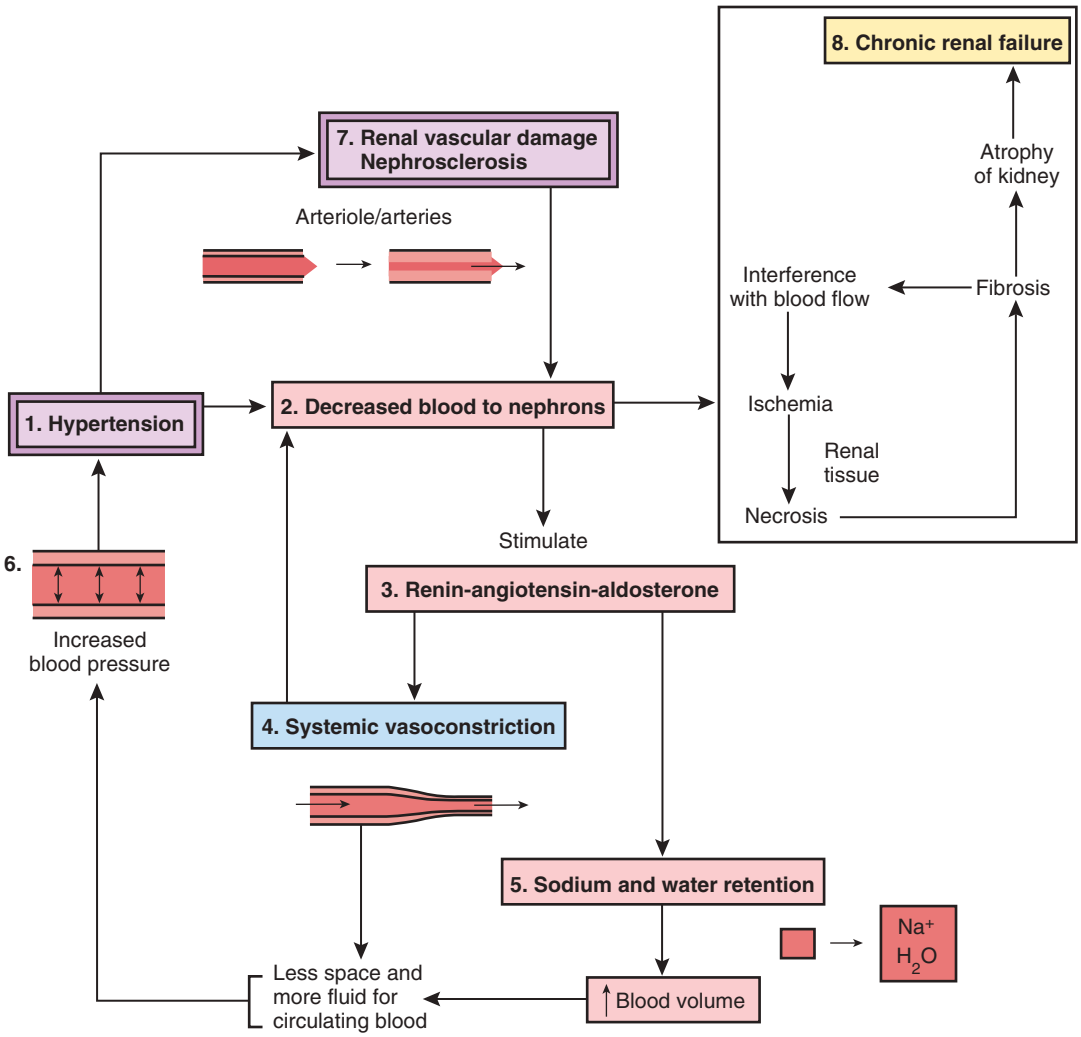


FIGURE 21-13 The relationship between hypertension and the kidney.

changes cause thickening and hardening of the walls of the arterioles and small arteries and narrowing or occlusion of the lumina of the blood vessels. Such changes reduce the blood supply to the kidney, causing ischemia and atrophy, and also stimulate the secretion of renin, ultimately increasing the blood pressure (Fig. 21-13). Continued ischemia can lead to gradual destruction of renal tissue and chronic renal failure. Often such damage is asymptomatic until a late stage.

It is often difficult to determine whether the primary lesion has developed in the kidney or it is secondary to essential hypertension (see Chapter 18), diabetes mellitus (see diabetic nephropathy and Fig. 25-6 in Chapter 25), or another condition. In any case, a vicious cycle can develop with the kidneys and hypertensive changes, and this must be broken to prevent renal failure or other complications of hypertension such as congestive heart failure.

Treatment

Drugs such as antihypertensive agents, diuretics, ACE inhibitors, and beta-blockers (which block renin release) all can assist in maintaining renal blood flow and reducing blood pressure. These drugs are discussed in Chapter 18 (see Table 18-1). Sodium intake should be reduced as well.

THINK ABOUT 21-15

Explain factors that may contribute to elevated blood pressure in the client with renal disease.

CONGENITAL DISORDERS

It is estimated that 10% of infants are born with an abnormality in the urinary system. Some examples follow:

- *Vesicoureteral reflux* is due to a defective valve in the bladder was mentioned under infections.

- *Agenesis* refers to a developmental failure of one kidney to develop. This is asymptomatic and usually is an incidental finding if diagnosed at all.
- *Hypoplasia,* or failure to develop to normal size, is often a unilateral defect. Sometimes it results from fibrosis in the kidney, rather than being a true developmental flaw.
- *Ectopic kidney* means that a kidney and its ureter are displaced out of normal position. A common location is lower in the abdominal or pelvic cavity. Kidney function is normal. In this position the ureter may become kinked, causing obstruction or infection.
- *Fusion* of the two kidneys during development is a common malformation, resulting in a single "horseshoe" kidney. Usually kidney function is normal.

ADULT POLYCYSTIC KIDNEY

The most common form of this genetic disease is transmitted as an autosomal dominant gene on chromosome 16. There are no indications in the child and young adult; the first manifestations usually appear around age 40 years, when chronic renal failure becomes symptomatic and dialysis is required. This condition is responsible for about 10% of the patients with end-stage chronic renal failure. In some cases, early diagnosis is possible when high blood pressure occurs and is difficult to control or when secondary polycythemia develops due to increased erythropoietin secretion. Diagnosis can be confirmed by an abdominal CT scan or MRI.

Multiple cysts develop in both kidneys and gradually expand over the years, first enlarging the kidneys, then compressing and destroying kidney tissue until chronic renal failure occurs (Fig. 21-14). In some cases, cysts are found in other organs such as the liver or cerebral aneurysms are found.

Polycystic disease in children is transmitted as a recessive gene and is manifest at birth. However, in this case, the child is either stillborn or dies during the first months.

WILMS' TUMOR (NEPHROBLASTOMA)

This is the most common tumor occurring in children, with approximately 400 children diagnosed in the United States annually. It is associated with defects in tumor-suppressor genes on chromosome 11 and may occur in conjunction with some other congenital disorders. It is usually unilateral. The tumor presents as a large encapsulated mass.

Wilms' tumor is usually diagnosed at ages 2 to 5 years, when the large abdominal mass becomes obvious (often a waistband on clothes does not fasten or a unilateral bulge appears). In some cases the child develops high blood pressure. Pulmonary metastases may be present at diagnosis.

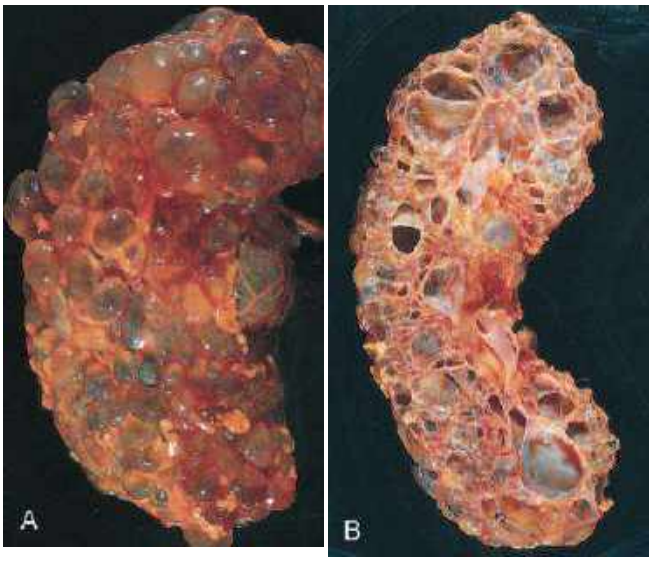


FIGURE 21-14 Polycystic kidney (adult autosomal dominant). **A**, External surface of enlarged kidney, showing cysts. **B**, Bisected, shows large interior cysts. *(From Kumar V, Abbas AK, Fausto M:* Robbins and Cotran Pathologic Basis of Disease, *7th ed. Philadelphia, WB Saunders, 2005.)*

The prognosis for the child depends on the histologic results as well as the stage of the tumor at diagnosis. Tumors showing a favorable histology (less aggressive) have an average survival rate of 90%; those with a less favorable pathology (more aggressive) have survival rates ranging from 80% to 40%.

RENAL FAILURE

ACUTE RENAL FAILURE

Pathophysiology

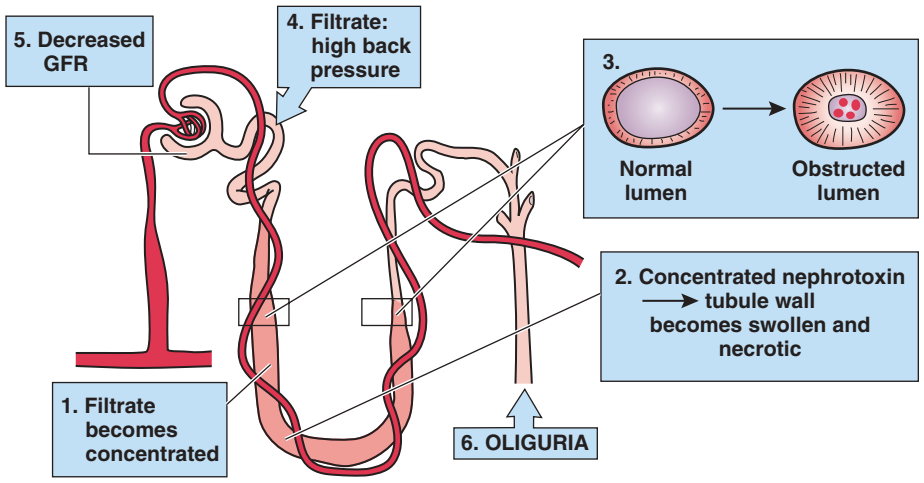
The kidneys may fail to function for many different reasons. Either directly reduced blood flow into the kidney or inflammation and necrosis of the tubules cause obstruction and back pressure, leading to greatly reduced GFR and **oliguria** (reduced urine output) or **anuria** (no urine output).

Both kidneys must be involved. The failure is usually reversible if the primary problem is treated successfully. Dialysis may be used to replace the kidney function during this period. In some cases, the kidneys sustain a degree of permanent damage.

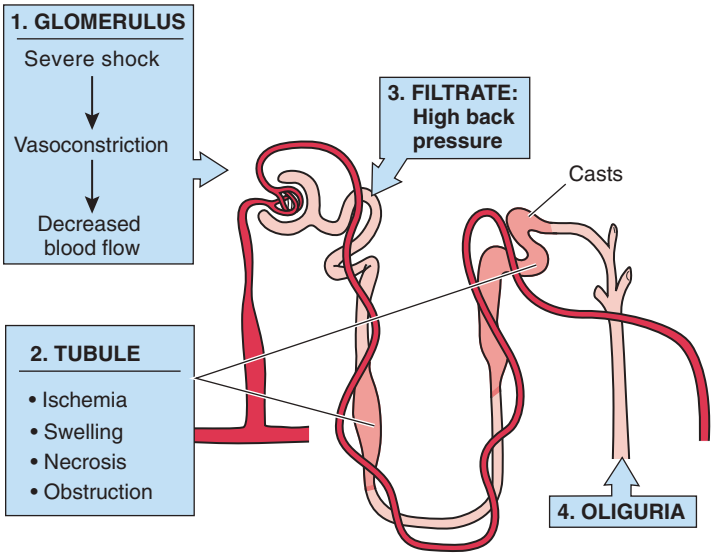
Etiology

Acute renal failure has numerous causes (Fig. 21-15):

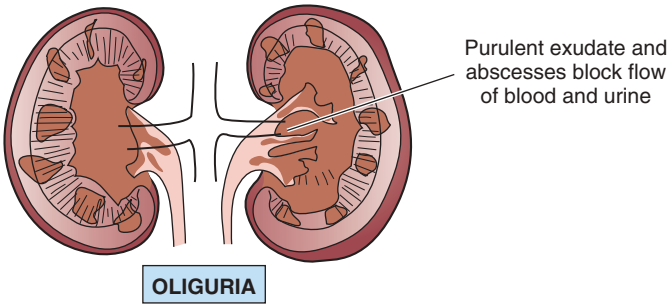
- Acute bilateral kidney disease, such as glomerulonephritis, which reduces GFR
- Severe and prolonged circulatory shock or heart failure, which results in tubule necrosis. Shock associated with burns or crush injuries or sepsis frequently causes renal failure. With burns, the damaged eryth-



A. NEPHROTOXINS



B. ISCHEMIA



C. PYELONEPHRITIS

FIGURE 21-15 Causes of acute renal failure. **A**, Nephrotoxins. **B**, Ischemia. **C**, Pyelonephritis.

rocytes break down in the circulation, releasing free hemoglobin that may accumulate in the tubules, causing obstruction. Hemoglobin also is toxic to tubule epithelium, causing inflammation and necrosis (see Chapter 2, Burns). When skeletal muscle is crushed in an accident, myoglobin is released with similar effects;

- *Nephrotoxins* such as drugs, chemicals, or toxins, which cause tubule necrosis and obstruction of blood flow. Industrial chemicals such as the solvent carbon tetrachloride may cause acute renal failure when exposure is intense. Long-term low-level exposures may cause gradual damage, eventually leading to chronic renal failure. The list of frequently used drugs possibly causing tubule damage is growing longer and now includes sulfa drugs, phenacetin, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen and aspirin, and penicillin. When patients take these drugs, fluid intake should be greatly increased to reduce the risk of kidney damage.
- Occasionally mechanical obstructions such as calculi, blood clots, or tumors, which block urine flow beyond the kidneys and cause acute renal failure

Signs and symptoms

Acute renal failure usually develops rapidly. Blood tests show elevated serum urea nitrogen (BUN) and creatinine as well as metabolic acidosis and hyperkalemia, confirming the failure of the kidneys to remove wastes.

Treatment

It is important to reverse the primary problem as quickly as possible to minimize the risk of necrosis and permanent kidney damage, with uremia (see chronic renal failure).

Dialysis may be used to normalize body fluids and maintain homeostasis during the *oliguric* stage. Recovery from acute renal failure is evidenced by increased urine output (*diuretic* stage). It may take a few months before the epithelium lining the renal tubules recovers totally, so fluid and electrolyte balance may not return to normal for some time.

THINK ABOUT 21-16

Focusing on the circulation through the nephron, explain why severely decreased blood flow in the afferent arteriole could cause tubule necrosis and obstruction.

CHRONIC RENAL FAILURE

Chronic renal failure is the gradual irreversible destruction of the kidneys over a long period of time. It may result from chronic kidney disease, such as bilateral pyelonephritis or congenital polycystic kidney disease, or from systemic disorders such as hypertension or diabetes. As mentioned, long-term exposure to nephrotoxins is a cause. The gradual loss of nephrons is asymptomatic until it is well advanced because the kidneys normally have considerable reserve function. Once advanced, the progress of chronic renal failure may be slowed but cannot be stopped because the scar tissue and loss of functional organization tend to cause further degenerative changes.

Pathophysiology

Chronic renal failure has several stages (Fig. 21-16), progressing from decreased renal reserve, to insufficiency, to end-stage renal failure or uremia. In the early stages of *decreased reserve* (around 60% nephrons lost) there is a decrease in GFR, serum creatinine levels that are consistently higher than average but within normal range, serum urea levels that are normal, and no apparent clinical signs. The remaining nephrons appear to adapt, increasing their capacity for filtration.

The second stage (around 75% nephrons lost), or that of *renal insufficiency,* is indicated by a change in blood chemistry and manifestations. At this point, GFR is decreased to approximately 20% of normal, and there is significant retention of nitrogen wastes (urea and creatinine) in the blood. Tubule function is decreased, resulting in failure to concentrate the urine and control the secretion and exchange of acids and electrolytes. Osmotic diuresis occurs as the remaining functional nephrons filter an increased solute load. This stage is marked by excretion of large volumes of dilute urine (low fixed specific gravity). Erythropoiesis is decreased, and the patient's blood pressure is elevated. The cardiovascular system must compensate for these effects (see Chapter 18).

Uremia, or *end-stage renal failure* (more than 90% nephrons lost), occurs when GFR is negligible. Fluid, electrolytes, and wastes are retained in the body, and all body systems are affected. In this stage, marked oliguria or anuria develops. Regular dialysis or a kidney transplant is required to maintain the patient's life. A comparison of acute and chronic renal failure may be found in Table 21-3.

Signs and symptoms

The *early* signs of chronic renal failure include:

- Increased urinary output (**polyuria**), manifested as frequency and nocturia
- General signs such as anorexia, nausea, anemia, fatigue, unintended weight loss, and exercise intolerance
- Bone marrow depression and impaired cell function caused by increased wastes and altered blood chemistry
- High blood pressure

As the kidneys fail completely (end-stage failure), *uremic* signs appear:

- Oliguria
- Dry, pruritic, and hyperpigmented skin, easy bruising
- Peripheral neuropathy—abnormal sensations in the lower limbs

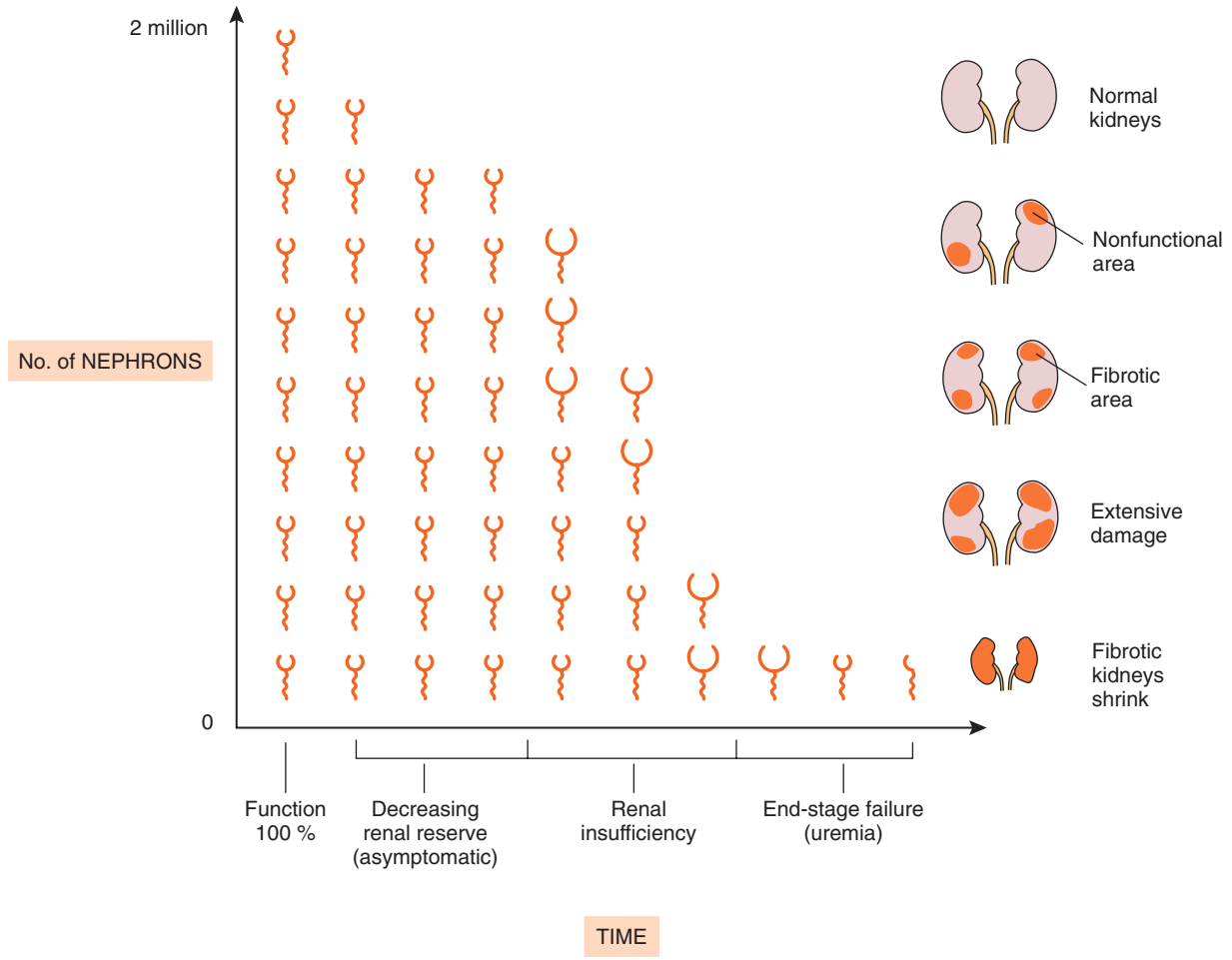


FIGURE 21-16 Development of chronic renal failure.

- Impotence and decreased libido in men, menstrual irregularities in women
- Encephalopathy (lethargy, memory lapses, seizures, tremors)
- Congestive heart failure, arrhythmias
- Failure of the kidney to activate vitamin D for calcium absorption and metabolism, combined with urinary retention of phosphate ion, leading to hypocalcemia and hyperphosphatemia with **osteodystrophy** (Fig. 21-17), osteoporosis, and tetany (see Chapters 25 and 26)
- Possibly uremic frost on the skin and a urinelike breath odor in the terminal stage or if infection is present
- Systemic infections such as pneumonia (common), owing to poor tissue resistance related to anemia, fluid retention, and low protein levels

Diagnostic tests

Anemia, acidosis, and **azotemia** are the key indicators of chronic renal failure.

1. Metabolic acidosis becomes decompensated (serum pH below 7.35) in the late stage as GFR declines and tubule function is lost (see Chapter 6).

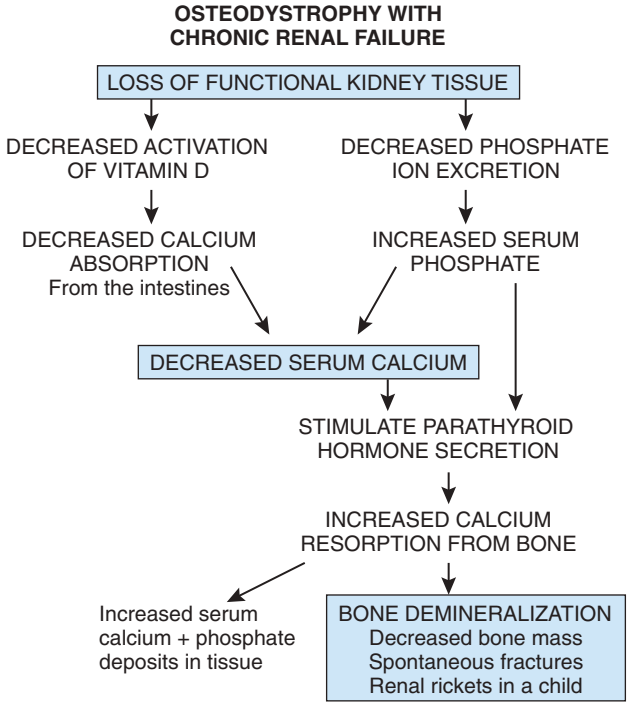


FIGURE 21-17 The development of osteodystrophy in chronic renal failure.

TABLE 21-3 Comparison of Acute Renal Failure and Chronic Renal Failure

Characteristic	Acute Renal Failure	Chronic Renal Failure
Causes	Severe shock Burns Nephrotoxins, massive exposure Acute bilateral kidney infection or inflammation	Nephrosclerosis Diabetes mellitus Nephrotoxins, long-term exposure Chronic bilateral kidney inflammation or infection Polycystic disease
Onset	Sudden, acute	Slow, insidious
Early signs	Oliguria, increased serum urea	Polyuria with dilute urine Anemia, fatigue, hypertension
Progressive signs	Recovery—increasing urine output If prolonged failure—uremia	End-stage failure or uremia Oliguria, acidosis, azotemia

2. Azotemia refers to the presence of nitrogen wastes in the blood, as indicated by elevated serum creatinine and urea levels.
3. Anemia becomes severe.
4. Serum electrolyte levels may vary depending on the amount of water retained in the body. Usually hyponatremia and hyperkalemia occur, as well as hypocalcemia and hyperphosphatemia.

Treatment

Chronic renal failure affects all body systems, as indicated earlier. It is difficult to maintain homeostasis of fluids, electrolytes, and acid-base balance. Drugs are available to stimulate erythropoiesis and reduce phosphate levels. As well, specific drugs may be required to treat hypertension, arrhythmias, heart failure, and other complications. Drug dosages need to be carefully considered and adjusted if necessary in patients with uremia because of the kidney's decreased ability to excrete drugs in a timely manner.

Clients are subject to many complications, which in turn affect the uremia. For instance, a simple infection increases the wastes in the body, compromising all body systems. Intake of fluid, electrolytes, and protein must be restricted because the kidneys are limited in their ability to excrete excess wastes and fluid. Children with kidney failure have retarded growth and renal rickets.

In the uremic stage, dialysis or a transplant is required. Organ transplants are discussed in Chapter 3.

Hematological Malignancies

Cancers arising from hematopoietic and lymphoid tissues are termed hematologic malignancies which include three main types: leukemia, lymphomas and multiple myeloma. Compared with solid malignancies, the growth rate of most hematologic malignancies is rapid and aggressive.

A) Leukemia

Leukemia is a group of blood cancers (hematologic malignancies) which are derived from cytogenetic alterations in blood-forming tissues (Hematopoietic stem cells, HSCs) and/or blood cells. These blood cells are not fully developed and are called blasts or leukemia cells. HSCs are multipotent stem cells originated in the bone marrow which give rise to all blood cells from the common myeloid progenitors (monocytes, neutrophils, basophils, eosinophils, erythrocytes, and platelets) and the common lymphoid progenitors (T-cells, B-cells, NK-cells, and NKT-cells). In general, leukemia is classified based on the type of blood cell affected (myeloid or lymphocytic), and the origin of the altered blood cell (acute or chronic).

- ***Myeloid (Myelogenous) leukemia*** include malignancies of myeloid cells: granulocytes (neutrophils, basophils, and eosinophils), monocytes, erythrocytes and platelets.
- ***Lymphocytic leukemia*** include malignancies of lymphoid cells as NK, T and B lymphocytes.

Acute leukemia is characterized by expansion and differentiation of immature hematopoietic stem cells which causes large numbers of early progenitor cells (blasts) to appear in the bone marrow. These leukemic blasts develop and lead to failure of the bone marrow to produce adequate numbers of functional mature blood cells. Acute leukemia is the most common type of cancer diagnosed in younger people. It progresses rapidly and is typically fatal within weeks or months if left untreated. It is classified according to the line of hematopoietic stem cells which are involved as the following:-

- ***Acute lymphocytic leukemia (ALL):*** It is a cancer of the lymphoid line of blood cells characterized by a rapid development of large numbers of immature lymphocytes (lymphoid blast cells), so it is known as acute lymphoblastic leukemia. It occurs mainly in children of 1–4 years old.

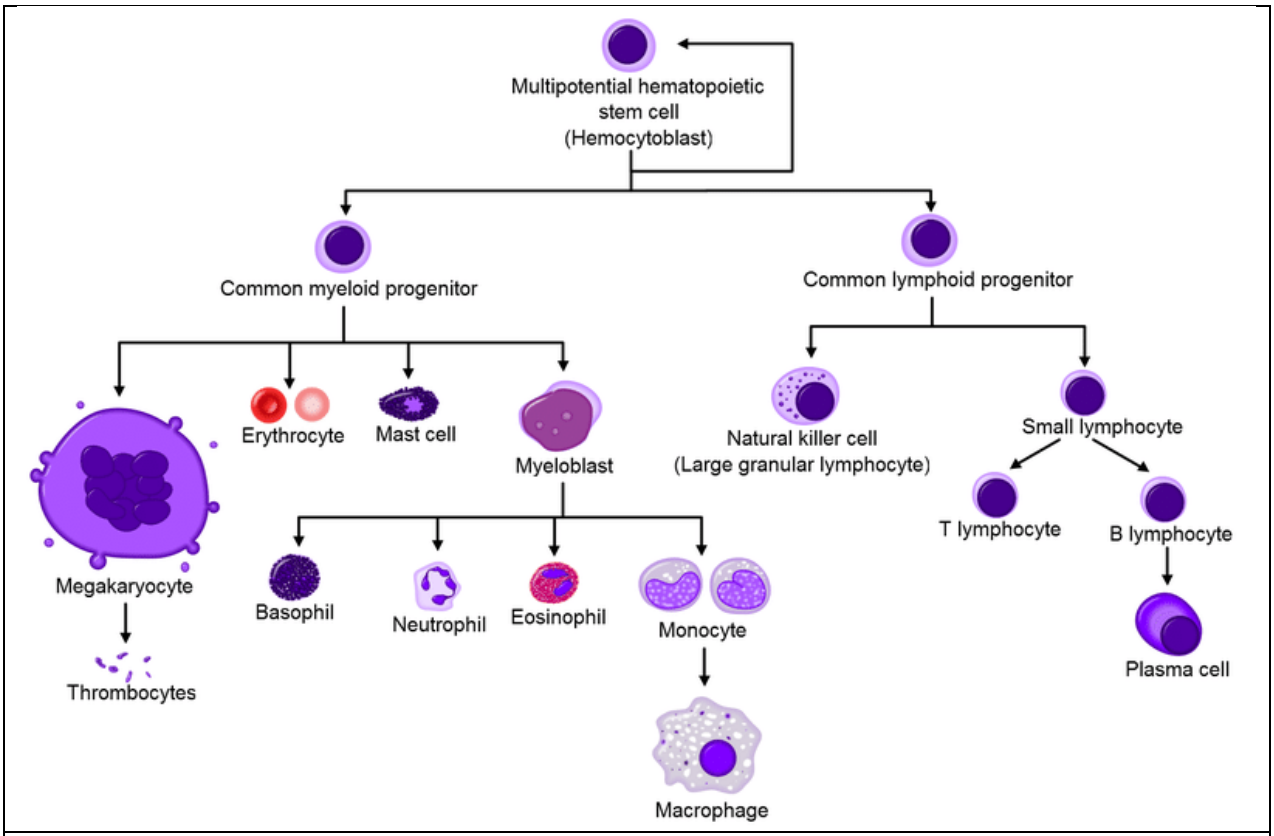
- ***Acute myeloid leukemia (AML):*** It is a cancer of the myeloid line of blood cells characterized by a rapid development of large numbers of immature myeloid (myeloid blast cells), so it is known as acute myeloblastic leukemia. It is occurs mainly in adults and becomes more common with age.

AML and ALL can be distinguished based on morphological examination of the bone marrow and peripheral blood by special cytochemical stains, surface membrane phenotyping, and chromosomal analysis.

Chronic leukemia

It is characterized by much higher rate of proliferation to produce large numbers of mature, but still abnormal, blood cells. Typically, it takes months or years to progress. Chronic leukemia mostly occurs in older people, but can occur at any age. It is classified according to the line of hematopoietic stem cells which are involved as the following:-

- ***Chronic lymphocytic leukemia*** (CLL) which is characterized by increased and unregulated growth of mature but abnormal lymphocytes.
- ***Chronic myeloid leukemia*** (CML) which is characterized by increased and unregulated growth of mature but abnormal granulocytes, and abnormal monocytes.



Differentiation of hematopoietic stem cells into different blood cells

Acute leukemia	Chronic leukemia
• affects immature blood cells	• usually affects mature cells
• occurs suddenly	• appears gradually
• develops quickly	• develops slowly over months to years
• includes acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML)	• includes chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML)

Causes and risk factors of leukemia

The definite causes of leukemia are not known, but damage of DNA of immature blood cells play a vital role in development of the disease. Some factors increase the risk of developing leukemia, including:

- Family history of leukemia
- Repeated exposure to radiation

- Previous treatment with chemotherapy or radiation for other forms of cancers
- Continuous exposure to some chemicals such as benzene, petroleum products, paints, and heavy metals
- Viral infections
- Genetic disorders, mainly Down syndrome
- Smoking

Signs and symptoms of leukemia

The main symptoms of leukemia are caused by continually increasing numbers of leukemia cells in the bone marrow, which reduces the number of normal blood cells. The signs include:

- Anemia due to the lack of red blood cells which can cause weakness, tiredness and breathlessness
- Repeated or persistent infections due to the lack of normal white blood cells which can cause mouth sores, sore throats, fever, sweat, and cough
- Increased bruising and bleeding due to the lack of platelets which can cause bruising without being bumped, nosebleeds, heavy periods in women and small red or purple spots on the skin
- Bone pain, chest pain weight loss, fatigue
- Enlarged lymph nodes and spleen

Diagnosis of leukemia

1. Complete blood count (CBC)
2. Imaging procedures as chest X-ray, CT scan, ultrasound and MRI to show leukemia's effects on such body parts as bones, brain, spleen, and liver
3. Bone marrow biopsy or aspiration: microscopic analysis, immunohistochemistry, genetic analysis and biomarkers.

Treatment of leukemia

Leukemia can be treated by chemotherapy, radiation, stem cell transplantation, and recently using immunotherapy.

1. Chemotherapy

Treatment for acute leukemia using chemotherapy is divided into two or three phases: *remission induction, consolidation and maintenance therapy*. Only patients with ALL are given maintenance treatment.

a. Remission induction therapy

Induction treatment is an intensive course of chemotherapy that lasts 4–6 weeks. It aims to kill as many leukemia cells as possible. In this phase, there should be less than 5% leukemic blasts in the bone marrow, presence of normal blood cells and absence of tumor cells from blood. The chemotherapy usually consists of a combination of three or four drugs given intravenously. Because cytotoxic drugs penetrate poorly to CNS, thus it act as sanctuary site for leukemic cells. Here the cells can grow, multiply and travel throughout the rest of the body in the blood stream. So, CNS prophylaxis must be given at this phase which usually consists of methotrexate plus cytarabine as intrathecal injection. Radiation therapy to the head (cranial irradiation) is also used.

b. Consolidation therapy

Consolidation treatment is used immediately after the remission induction therapy to destroy any remnant of leukemic cells and it lasts to one week. This is important to prevent disease relapse.

c. Maintenance therapy

The aim of maintenance therapy is to kill any residual cell that was not killed by remission induction and consolidation regimens, where it is used mainly in ALL. Although such cells are few, they will cause relapse if not eradicated. The length of maintenance therapy is 2-3 years.

2. Radiation therapy

3. Hematopoietic stem cell transplantation (HSCT)

HSCT is considered as the established therapy for hematological malignancies, in which stem cells from either bone marrow (BM), peripheral blood (PB) or umbilical cord blood (UCB) are infused into patients to establish the functions of bone marrow and immune system. Based on who gives the stem cells, HSCT is classified into autologous SCT (auto-SCT) and allogeneic SCT (allo-SCT). Before a stem cell transplant, the patient receives high doses of chemotherapy or radiation therapy to destroy the bone marrow.

4. Immunotherapy

Immunotherapy is used to enhance the immune system recognize and attack leukemia cells.

5. Targeted therapy

Targeted therapy uses drugs that attack specific antigen within cancer cells or immune cells.

B) Lymphoma

The lymphomas are a heterogeneous group of hematologic malignancies that originate in lymphoid tissues. A lymphoma may arise within lymph nodes or in lymph organs.

The two major types of lymphomas are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) where NHL is more common than HL (1:7). Both cancers originate in the lymphoid tissue and may similar symptoms, but the conditions themselves are different. There are key differences between Hodgkin's and non-Hodgkin's lymphoma as the following:-

1. NHL is more common than HL.

2. In NHL, either B cells or T cells are involved, while in HL B cells are mainly involved.

3. NHL occurs more frequently in older people (above 55 years), while HL occurs most commonly in younger people between 15 and 35 years.

4. The morphology of the NHL cells differs from the cells of HL, where HL has certain type of cells termed as Reed-Sternberg cells. These are large cancerous cells that have more than one nucleus (either multinucleated or bilobed nucleus).

5. The malignant cells in HL usually remain localized in one lymph node or the surrounding area in the neck (the main site), shoulder and chest, while NHL tend to develop in peripheral lymph nodes and spread throughout the body.

6. HL is one of the most curable cancers with a cure rate between 60 and 90%, while NHL is poor and depends on the grade of tumor involved.

7. Epstein-Barr virus (EBV) is present in about 50 % of HL tumors while it is seldom seen in NHL.

Signs and symptoms of lymphoma

Both Hodgkin's and non-Hodgkin's lymphoma nearly have similar symptoms as the following:

- The most common symptom of both cancers is swelling the lymph nodes in neck, under the arms or in groin.
- Unexplained fevers
- Heavy sweating, particularly at night
- Weight loss
- Persistent fatigue
- Rash or itching
- Cough and breathlessness
- Abdominal pain and vomiting

Diagnosis of lymphoma

1. Physical exam for the lymph nodes in neck, under arms and groin to ensure if they are swollen.
2. Complete blood count (CBC) will usually be performed to check the number of white blood cells.
3. Imaging procedures as chest X-ray, CT scan, ultrasound and MRI.
4. Biopsy from the lymph nodes and bone marrow.

Treatment of lymphoma

Lymphoma can be treated by chemotherapy, radiation, stem cell transplantation, and recently using immunotherapy.

Breast cancer

Breast cancer is a malignant tumor that starts in the cells of the breast. It occurs exclusively in women, but men can get it too.
The female breast is made up of lobes, ducts and stroma (fatty tissue and connective tissue surrounding the ducts and lobules). Each breast has 15 to 20 sections called lobes, which have many smaller sections called lobules. Lobules end in dozens of tiny bulbs that can make milk. The lobes, lobules, and bulbs are linked by thin tubes called ducts that carry the milk from the lobules to the nipple.

Malignant breast tumors

Most malignant breast tumors begin in the cells that line the ducts (ductal carcinoma) and some begin in the lining cells of lobules (lobular carcinoma), while a small number start in other tissues.

- ***Carcinoma in situ:*** This term is used for an early stage of cancer, when it is limited to the layer of cells where it began. In breast cancer, *in situ* means that the cancer cells have not grown into deeper tissues in the breast (pre-invasion) or spread to other organs in the body (no metastasis). Carcinoma in situ of the breast is referred to as non-invasive cancer and it can develop into an invasive breast cancer if left untreated. Most breast cancers are invasive carcinomas either invasive ductal carcinoma or invasive lobular carcinoma.

1. Ductal carcinoma in situ

Ductal carcinoma in situ (DCIS), also known as intraductal carcinoma, is the most common type of non-invasive breast cancer. DCIS means that the cancer cells grow inside the ducts and do not spread through the walls of the ducts into the surrounding breast tissue. Nearly all women diagnosed at this early stage of breast cancer can be cured. A mammogram is often the best way to find DCIS early.

2. Lobular carcinoma in situ

In lobular carcinoma in situ (LCIS), the cancer cells grow in the lobules of the milk-producing glands of the breast, and they do not spread through the wall of the lobules into the surrounding breast tissue.

3. Invasive ductal carcinoma

Invasive ductal carcinoma (IDC) is the most common type of breast cancer *(about 8 of 10 invasive breast cancers are IDC)* which starts in a milk duct of the breast. Then, the cancer cells infiltrate through the wall of the duct and grows into the surrounding fatty tissue of the breast. At this point, they may be able to spread (metastasize) to other parts of the body through the lymphatic system and bloodstream.

4. Invasive lobular carcinoma

Invasive lobular carcinoma (ILC) starts in the milk-producing glands (lobules). Like IDC, it can metastasize to other parts of the body. About 1 invasive breast cancer in 10 is an ILC. Invasive lobular carcinoma may be harder to detect by a mammogram than invasive ductal carcinoma.

5. Inflammatory breast cancer

Inflammatory breast cancer (IBC) is uncommon type of invasive breast cancer and accounts for about 1% to 3% of all breast cancers. Usually there is no single lump, but the skin on the breast look red, thick, pitted appearance and feel warm. These changes are not caused by inflammation or infection, but by cancer cells blocking lymph vessels in the skin.

6. Triple-negative breast cancer

This term is used to describe breast cancers (usually invasive ductal carcinomas) whose cells lack estrogen receptors, progesterone receptors and human epidermal growth factor type 2 receptor (HER2) on their surfaces. It tends to occur more often in younger women and in African-American women. Because the tumor cells lack these certain receptors, neither hormone therapy nor drugs that target HER2 are effective treatments.

Risk factors of breast cancer

1. Age and gender: Most advanced breast cancer cases are found in women over age 50. Women are 100 times more likely to get breast cancer than men.

2. Family history: Women may have a higher risk for breast cancer if they have a close relative who has had breast, uterine, or ovarian cancer. About 20 - 30% of women with breast cancer have a family history of the disease (BRCA1, 2 genes).

3. Personal history of breast cancer: A woman with cancer in one breast has a 3 to 4 fold increased risk of developing a new cancer in the other breast or in another part of the same breast.

4. Menstrual cycle: Women who got their periods early (before age 12) or went through menopause late (after age 55) have an increased risk for breast cancer.

5. Childbirth: Women who have never had children or who had them only after age 35 have an increased risk for breast cancer.

6. Hormone replacement therapy (HRT) or oral contraceptives: Women have a higher risk for breast cancer if they have received hormone therapy with estrogen for long periods.

7. Obesity: Obesity has been linked to breast cancer because obese women produce more estrogen.

8. Radiation: If women received radiation therapy as a child or young adult to treat cancer of the chest area, they have a much higher risk for developing breast cancer. The younger they received radiation and the higher the dose, the higher risk of breast cancer.

9. Benign breast tumor: Benign breast tumor can develop into malignant breast tumor if it is not treated.

Signs and symptoms

- The most common symptom of breast cancer is painless (when present deeply, painful superficially) hard mass that has irregular edges, but sometimes it can be soft, and rounded.
- Swelling of all or part of the breast (even if no distinct lump is felt)
- Skin dimpling
- Breast or nipple pain
- Nipple retraction (turning inward)
- Redness, or thickening of the nipple or breast skin
- Nipple discharge (may be bloody, clear to yellow, green and look like pus)
- Skin ulcers
- Swelling of one arm (beside the breast with cancer)

Stages of breast cancer

There are many systems used for staging breast cancer depending on its progression, one of them as the following:-

a. Stage 0: Ductal or lobular carcinoma in situ which almost is completely curable.

b. Stage 1: The tumor measures less than 2cm. The lymph nodes in the axilla are not affected and there are no signs that the cancer has spread elsewhere in the body.

c. Stage 2: The tumor measures between 2 and 5cm or the lymph nodes in the axilla are affected, or both. However, there are no signs that the cancer has spread further.

d. Stage 3: The tumor is larger than 5cm and may be attached to surrounding structures such as the muscle or skin. The lymph nodes are usually affected.

e. Stage 4: The tumor is of any size, the lymph nodes are usually affected and the cancer has spread to other parts of the body.

Diagnosis of breast cancer

1. Breast self-exam (BSE)

Women should report any breast changes to a health professional as soon as these changes are found. Finding a breast change does not necessarily mean there is a cancer.

2. Clinical breast exam

Clinical breast exam (CBE) is an exam of the breast by a doctor or other health professional. The doctor will carefully feel the breasts and under the arms for lumps or anything else that seems unusual as size, shape or changes in the skin of the breasts or nipple. It is annually for women over 40 years and at least every 3 years for women between 20 and 40 years.

3. Mammography

Mammography is the process of using low-energy X-rays to examine the human breast. The goal of mammography is the early detection of breast cancer, typically through detection of

characteristic masses and/or microcalcifications. It can be done every year or every two years for women more than 45 years.

4. Breast ultrasound

Ultrasound, also known as sonography, is a procedure in which high-energy sound waves are used to outline internal tissues or organs and make echoes. Usually, breast ultrasound is used to check abnormal result found on the mammogram. Ultrasound can distinguish between cysts (fluid-filled sacs) and solid masses.

5. Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a procedure that uses a magnetic radio waves to make a very detailed picture of areas inside the body. MRI can be used to better examine doubtful areas found by a mammogram. It is also used for women with breast cancer to determine the actual size of the cancer and to look for any other cancers in the breast.

6. Biopsy

Biopsy is done when mammograms or other imaging tests find a breast change or abnormality that is possibly cancer. A biopsy is the best way to tell if the cancer is really present. There are four types of biopsies as follows:

- Excisional biopsy: The removal of an entire lump of tissue.
- Incisional biopsy: The removal of part of a lump or a sample of tissue.
- Core biopsy: The removal of tissue using a wide needle.
- Fine-needle aspiration (FNA) biopsy: The removal of tissue or fluid, using a thin needle.

7. Immunohistochemistry

A method is used to measure the amount of estrogen, progesterone and HER2 receptors in the cancer tissue. If there are more receptors than normal, the cancer can grow more quickly and is more likely to spread to other parts of the body.

8. Tumor markers

The main tumor markers of breast cancer are CA-15-3 and CA-27-29.

Treatment of breast cancer

Cancer treatment may be local or systemic. Local treatment involve only the area of disease as surgery and radiation. Systemic treatment affect the entire body as anti-cancer drugs. The main types of treatment for breast cancer are:

1. Surgery
2. Radiation therapy
3. Anticancer drugs (Chemotherapy, Hormone therapy, Targeted therapy)

1. Surgery

Most patients with breast cancer will be treated with surgery to remove the cancer from the breast. Some of the lymph nodes under the arm are usually taken out and looked at under a

microscope to see if they contain cancer cells. All or part of the breast tissue may be removed depending on its type and stage as the following:

- ***Breast-conserving surgery***: is an operation to remove the cancer but not the breast itself. This process includes the following:

  a. Lumpectomy: Surgery to remove a tumor and a small amount of normal tissue around it.

  b. Partial mastectomy: Surgery to remove the part of the breast that has cancer and some normal tissue around it. The lining over the chest muscles below the cancer may also be removed. This procedure is also called a segmental mastectomy.

- ***Total mastectomy:*** Surgery to remove the whole breast that has cancer. This procedure is also called a simple mastectomy. Some of the lymph nodes under the arm may be removed for biopsy at the same time as the breast surgery or after.

- ***Modified radical mastectomy***: Surgery to remove the whole breast that has cancer, many of the lymph nodes under the arm, the lining over the chest muscles, and sometimes, part of the chest wall muscles.

2. Radiation therapy

Radiation therapy is treatment with high-energy rays or particles that destroy cancer cells. Radiation to the breast is often given after breast-conserving surgery and mastectomy to lower the chance that the cancer will come back.

- *External radiation therapy* uses a machine outside the body to send radiation toward the cancer.
- *Internal radiation therapy* uses a radioactive substance sealed in needles that are placed directly into or near the cancer.

3. Anticancer drugs

a. *Chemotherapy*, TAC: paclitaxel, doxorubicin (Adriamycin), and cyclophosphamide; CMF: cyclophosphamide, methotrexate, and 5-fluorouracil

b. *Hormonal therapy:* Tamoxifen and Aromatase inhibitors (AIs)

c. Targeted therapy: Trastuzumab (monoclonal antibody of HER2).