

# CHAPTER 17

## The Digestion and Absorption of Food

### **Overview: Functions of the Gastrointestinal Organs**

#### **Structure of the Gastrointestinal Tract Wall**

#### **Digestion and Absorption**

Carbohydrate  
Protein  
Fat  
Vitamins  
Water and Minerals

### **Regulation of Gastrointestinal Processes**

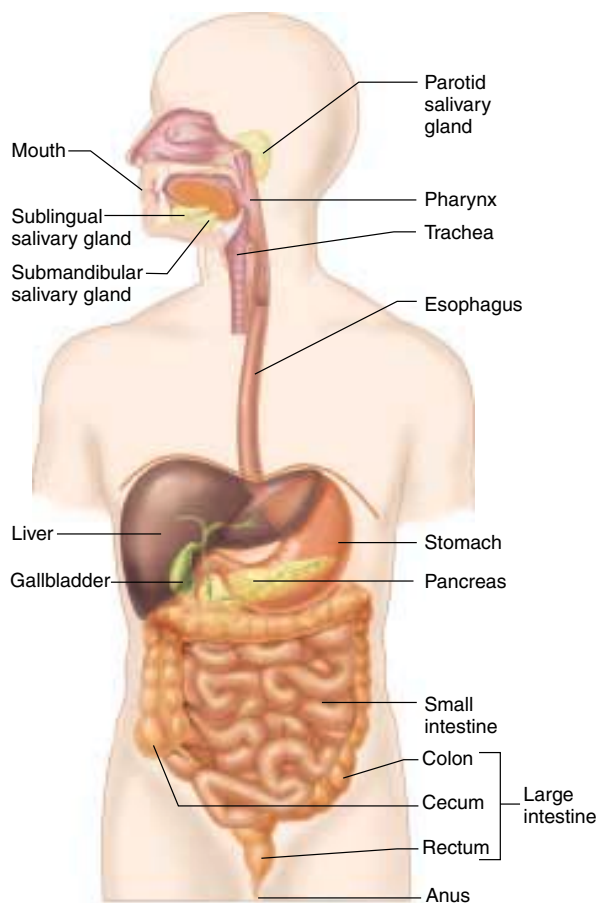
Basic Principles  
Mouth, Pharynx, and Esophagus  
Stomach  
Pancreatic Secretions  
Bile Secretion  
Small Intestine  
Large Intestine

### **Pathophysiology of the Gastrointestinal Tract**

Ulcers  
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Gallstones  
Lactose Intolerance  
Constipation and Diarrhea  
SUMMARY  
KEY TERMS  
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The **gastrointestinal (GI) system** (Figure 17-1) includes the **gastrointestinal tract** (mouth, pharynx, esophagus, stomach, small intestine, and large intestine) plus the accessory organs (salivary glands, liver, gallbladder, and pancreas) that are not part of the tract but secrete substances into it via connecting ducts. The overall function of the gastrointestinal system is to process ingested foods into molecular forms that are then transferred, along with salts and water to the body's internal environment, where they can be distributed to cells by the circulatory system.

The adult gastrointestinal tract is a tube approximately 15 ft long, running through the body from mouth to anus. The lumen of the tract, like the hole in a doughnut, is continuous with the external environment, which means that its contents are technically outside the body. This fact is



**FIGURE 17-1**

Anatomy of the gastrointestinal system. The liver overlies the gallbladder and a portion of the stomach, and the stomach overlies part of the pancreas. ✂

relevant to understanding some of the tract's properties. For example, the large intestine is inhabited by billions of bacteria, most of which are harmless and even beneficial in this location. However, if the same bacteria enter the internal environment, as may happen, for example, in the case of a ruptured appendix, they may cause a severe infection.

Most food enters the gastrointestinal tract as large particles containing macromolecules, such as proteins and polysaccharides, which are unable to cross the intestinal epithelium. Before ingested food can be absorbed, therefore, it must be dissolved and broken down into small molecules. This dissolving and breaking-down process—**digestion**—is accomplished by the action of hydrochloric acid in the stomach, bile from the liver, and a variety of digestive enzymes that are released by the system's exocrine glands. Each of these substances is released into the lumen of the GI tract by the process of **secretion**.

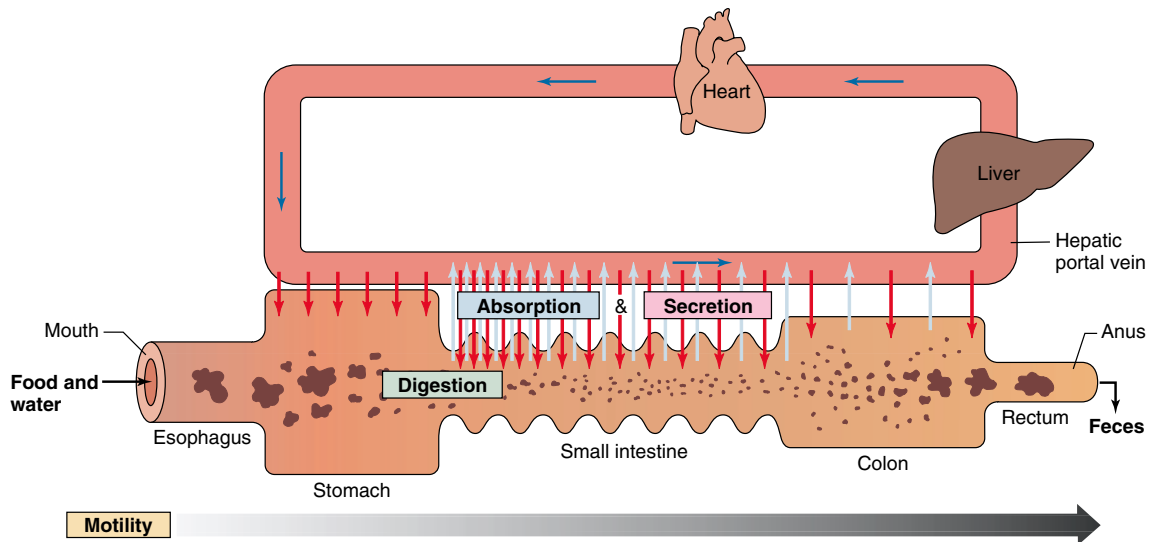
The molecules produced by digestion then move from the lumen of the gastrointestinal tract across a layer of epithelial cells and enter the blood or lymph. This process is called **absorption**.

While digestion, secretion, and absorption are taking place, contractions of smooth muscles in the gastrointestinal tract wall serve two functions; they mix the luminal contents with the various secretions, and they move the contents through the tract from mouth to anus. These contractions are referred to as the **motility** of the gastrointestinal tract.

The functions of the gastrointestinal system can be described in terms of these four processes—digestion, secretion, absorption, and motility (Figure 17-2)—and the mechanisms controlling them.

The gastrointestinal system is designed to maximize absorption, and within fairly wide limits it will absorb as much of any particular substance as is ingested. With a few important exceptions (to be described later), therefore, the gastrointestinal system does *not regulate* the amount of nutrients absorbed or their concentrations in the internal environment. The regulation of the plasma concentration of the absorbed nutrients is primarily the function of the kidneys (Chapter 16) and a number of endocrine glands (Chapter 18).

Small amounts of certain metabolic end products are excreted via the gastrointestinal tract, primarily by way of the bile, but the elimination of most of the body's waste products is achieved by the lungs and kidneys. The material—**feces**—leaving the system at the end of the gastrointestinal tract consists almost entirely of bacteria and ingested material that was neither digested nor absorbed—that is, material that was never actually part of the internal environment.



**FIGURE 17-2**

Four processes carried out by the gastrointestinal tract: digestion, secretion, absorption, and motility.

## Overview: Functions of the Gastrointestinal Organs

Figure 17-3 presents an overview of the secretions and functions of the gastrointestinal organs. The gastrointestinal tract begins with the **mouth**, and digestion starts there with chewing, which breaks up large pieces of food into smaller particles that can be swallowed. **Saliva**, secreted by three pairs of **salivary glands** (see Figure 17-1) located in the head, drains into the mouth through a series of short ducts. Saliva, which contains mucus, moistens and lubricates the food particles before swallowing. It also contains the enzyme **amylase**, which partially digests polysaccharides. A third function of saliva is to dissolve some of the food molecules. Only in the dissolved state can these molecules react with chemoreceptors in the mouth, giving rise to the sensation of taste (Chapter 9).

The next segments of the tract, the **pharynx** and **esophagus**, contribute nothing to digestion but provide the pathway by which ingested materials reach the stomach. The muscles in the walls of these segments control swallowing.

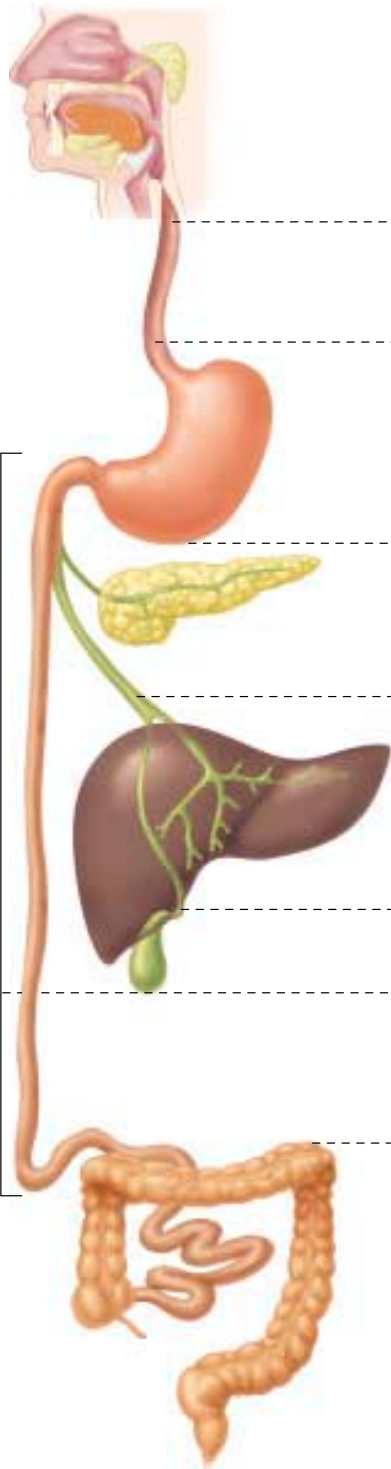
The **stomach** is a saclike organ, located between the esophagus and the small intestine. Its functions are to store, dissolve, and partially digest the macromolecules in food and to regulate the rate at which the stomach's contents empty into the small intestine. The glands lining the stomach wall secrete a strong acid, **hydrochloric acid**, and several protein-digesting enzymes collectively known as **pepsin** (actually a precursor of pepsin known as **pepsinogen** is secreted and converted to pepsin in the lumen of the stomach).

The primary function of hydrochloric acid is to dissolve the particulate matter in food. The acid environment in the **gastric** (adjective for "stomach") lumen alters the ionization of polar molecules, especially proteins, disrupting the extracellular network of connective-tissue proteins that form the structural framework of the tissues in food. The proteins and polysaccharides released by hydrochloric acid's dissolving action are partially digested in the stomach by pepsin and amylase, the latter contributed by the salivary glands. A major food component that is not dissolved by acid is fat.

Hydrochloric acid also kills most of the bacteria that enter along with food. This process is not 100 percent effective, and some bacteria survive to take up residence and multiply in the gastrointestinal tract, particularly the large intestine.

The digestive actions of the stomach reduce food particles to a solution known as **chyme**, which contains molecular fragments of proteins and polysaccharides, droplets of fat, and salt, water, and various other small molecules ingested in the food. Virtually none of these molecules, except water, can cross the epithelium of the gastric wall, and thus little absorption of organic nutrients occurs in the stomach.

Digestion's final stages and most absorption occur in the next section of the tract, the **small intestine**, a tube about 1.5 inches in diameter and 9 ft in length that leads from the stomach to the large intestine. Here molecules of intact or partially digested carbohydrates, fats, and proteins are broken down by hydrolytic enzymes into monosaccharides, fatty acids, and amino acids. Some of these enzymes are on the



Organ	Exocrine secretions	Functions
Mouth and pharynx		Chewing begins; initiation of swallowing reflex
Salivary glands	Salt and water	Moisten food
	Mucus	Lubrication
	Amylase	Polysaccharide-digesting enzyme
Esophagus		Move food to stomach by peristaltic waves
	Mucus	Lubrication
Stomach		Store, mix, dissolve, and continue digestion of food; regulate emptying of dissolved food into small intestine
	HCl	Solubilization of food particles; kill microbes
	Pepsin	Protein-digesting enzyme
	Mucus	Lubricate and protect epithelial surface
Pancreas		Secretion of enzymes and bicarbonate; also has nondigestive endocrine functions
	Enzymes	Digest carbohydrates, fats, proteins, and nucleic acids
	Bicarbonate	Neutralize HCl entering small intestine from stomach
Liver		Secretion of bile; many other nondigestive functions
	Bile salts	Solubilize water-insoluble fats
	Bicarbonate	Neutralize HCl entering small intestine from stomach
	Organic waste products and trace metals	Elimination in feces
Gallbladder		Store and concentrate bile between meals
Small intestine		Digestion and absorption of most substances; mixing and propulsion of contents
	Enzymes	Food digestion
	Salt and water	Maintain fluidity of luminal contents
Large intestine	Mucus	Lubrication
		Storage and concentration of undigested matter; absorption of salt and water; mixing and propulsion of contents; defecation
	Mucus	Lubrication

**FIGURE 17-3** Functions of the gastrointestinal organs. ✎

luminal surface of the intestinal lining cells, while others are secreted by the pancreas and enter the intestinal lumen. The products of digestion are absorbed across the epithelial cells and enter the blood and/or lymph. Vitamins, minerals, and water, which do not require enzymatic digestion, are also absorbed in the small intestine.

The small intestine is divided into three segments: An initial short segment, the **duodenum**, is followed by the **jejunum** and then by the longest segment, the **ileum**. Normally, most of the chyme entering from the stomach is digested and absorbed in the first quarter of the small intestine, in the duodenum and jejunum.

Two major glands—the pancreas and liver—secrete substances that flow via ducts into the duodenum. The **pancreas**, an elongated gland located behind

the stomach, has both endocrine (Chapter 18) and exocrine functions, but only the latter are directly involved in gastrointestinal function and are described in this chapter. The exocrine portion of the pancreas secretes (1) digestive enzymes and (2) a fluid rich in bicarbonate ions. The high acidity of the chyme coming from the stomach would inactivate the pancreatic enzymes in the small intestine if the acid were not neutralized by the bicarbonate ions in the pancreatic fluid.

The **liver**, a large gland located in the upper right portion of the abdomen, has a variety of functions, which are described in various chapters. This is a convenient place to provide, in Table 17–1, a comprehensive reference list of these **hepatic** (the term means “pertaining to the liver”) functions and the chapters in which they are described. We will be concerned in this

**TABLE 17–1 Summary of Liver Functions**

**A. Exocrine (digestive) functions (Chapter 17)**

1. Synthesizes and secretes bile salts, which are necessary for adequate digestion and absorption of fats.
2. Secretes into the bile a bicarbonate-rich solution, which helps neutralize acid in the duodenum.

**B. Endocrine functions**

1. In response to growth hormone, secretes insulin-like growth factor I (IGF-I), which promotes growth by stimulating cell division in various tissues, including bone (Chapter 18).
2. Contributes to the activation of vitamin D (Chapter 16).
3. Forms triiodothyronine ( $T_3$ ) from thyroxine ( $T_4$ ) (Chapter 10).
4. Secretes angiotensinogen, which is acted upon by renin to form angiotensin I (Chapter 16).
5. Metabolizes hormones (Chapter 10).
6. Secretes cytokines involved in immune defenses (Chapter 20).

**C. Clotting functions**

1. Produces many of the plasma clotting factors, including prothrombin and fibrinogen (Chapter 14).
2. Produces bile salts, which are essential for the gastrointestinal absorption of vitamin K, which is, in turn, needed for production of the clotting factors (Chapter 14).

**D. Plasma proteins**

1. Synthesizes and secretes plasma albumin (Chapter 14), acute phase proteins (Chapter 20), binding proteins for various hormones (Chapter 10) and trace elements (Chapter 14), lipoproteins (Chapter 18), and other proteins mentioned elsewhere in this table.

**E. Organic metabolism (Chapter 18)**

1. Converts plasma glucose into glycogen and triacylglycerols during absorptive period.
2. Converts plasma amino acids to fatty acids, which can be incorporated into triacylglycerols during absorptive period.
3. Synthesizes triacylglycerols and secretes them as lipoproteins during absorptive period.
4. Produces glucose from glycogen (glycogenolysis) and other sources (gluconeogenesis) during postabsorptive period and releases the glucose into the blood.
5. Converts fatty acids into ketones during fasting.
6. Produces urea, the major end product of amino acid (protein) catabolism, and releases it into the blood.

**F. Cholesterol metabolism (Chapter 18)**

1. Synthesizes cholesterol and releases it into the blood.
2. Secretes plasma cholesterol into the bile.
3. Converts plasma cholesterol into bile salts.

**G. Excretory and degradative functions**

1. Secretes bilirubin and other bile pigments into the bile (Chapter 17).
2. Excretes, via the bile, many endogenous and foreign organic molecules as well as trace metals (Chapter 20).
3. Biotransforms many endogenous and foreign organic molecules (Chapter 20).
4. Destroys old erythrocytes (Chapter 14).

chapter only with the liver's exocrine functions that are directly related to the secretion of **bile**.

Bile contains bicarbonate ions, cholesterol, phospholipids, bile pigments, a number of organic wastes and—most important—a group of substances collectively termed **bile salts**. The bicarbonate ions, like those from the pancreas, help neutralize acid from the stomach, while the bile salts, as we shall see, solubilize dietary fat. These fats would otherwise be insoluble in water, and their solubilization increases the rates at which they are digested and absorbed.

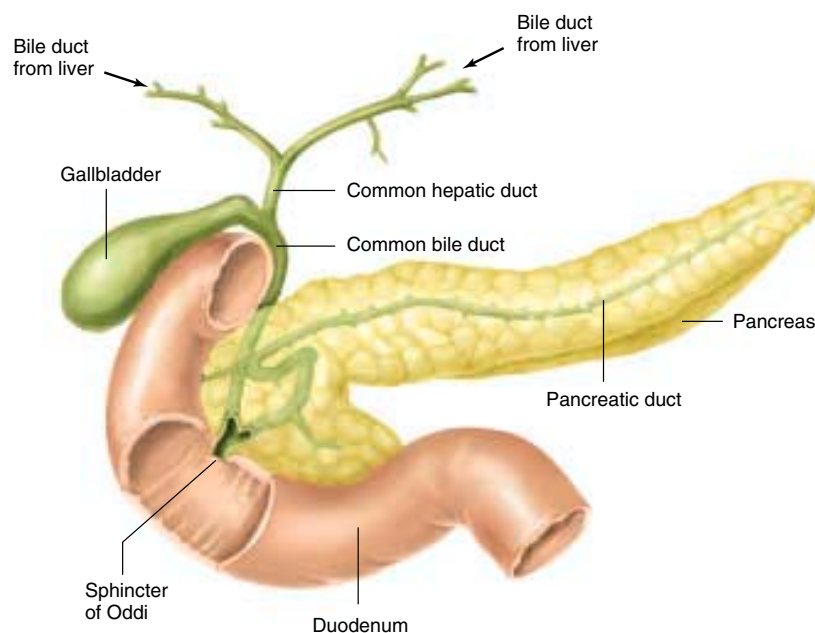
Bile is secreted by the liver into small ducts that join to form a single duct called the common hepatic duct. Between meals, secreted bile is stored in the **gallbladder**, a small sac underneath the liver that branches from the common hepatic duct. The gallbladder concentrates the organic molecules in bile by absorbing salts and water. During a meal, the smooth muscles in the gallbladder wall contract, causing a concentrated bile solution to be injected into the duodenum via the **common bile duct** (Figure 17-4), an extension of the common hepatic duct. The gallbladder can be surgically removed without impairing bile secretion by the liver or its flow into the intestinal tract. In fact, many animals that secrete bile do not have a gallbladder.

In the small intestine, monosaccharides and amino acids are absorbed by specific transporter-mediated

processes in the plasma membranes of the intestinal epithelial cells, whereas fatty acids enter these cells by diffusion. Most mineral ions are actively absorbed by transporters, and water diffuses passively down osmotic gradients.

The motility of the small intestine, brought about by the smooth muscles in its walls, (1) mixes the luminal contents with the various secretions, (2) brings the contents into contact with the epithelial surface where absorption takes place, and (3) slowly advances the luminal material toward the large intestine. Since most substances are absorbed in the small intestine, only a small volume of water, salts, and undigested material is passed on to the **large intestine**. The large intestine temporarily stores the undigested material (some of which is metabolized by bacteria) and concentrates it by absorbing salts and water. Contractions of the **rectum**, the final segment of the large intestine, and relaxation of associated sphincter muscles expel the feces—**defecation**.

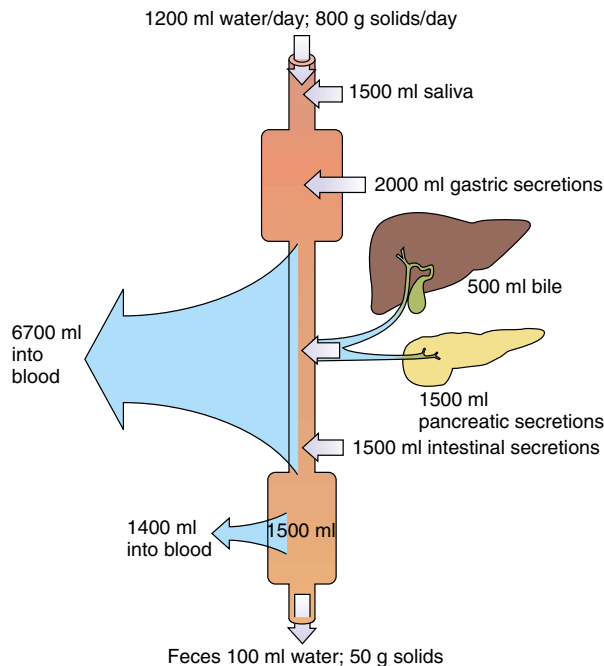
The average adult consumes about 800 g of food and 1200 ml of water per day, but this is only a fraction of the material entering the lumen of the gastrointestinal tract. An additional 7000 ml of fluid from salivary glands, gastric glands, pancreas, liver, and intestinal glands is secreted into the tract each day (Figure 17-5). Of the 8 L of fluid entering the



**FIGURE 17-4**

Bile ducts from the liver converge to form the common hepatic duct, from which branches the duct leading to the gallbladder. Beyond this branch, the common hepatic duct becomes the common bile duct. The common bile duct and the pancreatic duct converge and empty their contents into the duodenum at the sphincter of Oddi. ✎





**FIGURE 17-5**

Average amounts of solids and fluid ingested, secreted, absorbed, and excreted from the gastrointestinal tract daily.

tract, 99 percent is absorbed; only about 100 ml is normally lost in the feces. This small amount of fluid loss represents only 4 percent of the total fluids lost by the body each day (most fluid loss is via the kidneys and respiratory system). Almost all the salts in the secreted fluids are also reabsorbed into the blood. Moreover, the secreted digestive enzymes are themselves digested, and the resulting amino acids are absorbed into the blood.

This completes our overview of the gastrointestinal system. Since its major task is digestion and absorption, we begin our more detailed description with these processes. Subsequent sections of the chapter will then describe, organ by organ, regulation of the secretions and motility that produce the optimal conditions for digestion and absorption. A prerequisite for this physiology, however, is a knowledge of the structure of the gastrointestinal tract wall.

## Structure of the Gastrointestinal Tract Wall

From the midesophagus to the anus, the wall of the gastrointestinal tract has the general structure illustrated in Figure 17-6. Most of the tube's luminal surface is highly convoluted, a feature that greatly

increases the surface area available for absorption. From the stomach on, this surface is covered by a single layer of epithelial cells linked together along the edges of their luminal surfaces by tight junctions.

Included in this epithelial layer are exocrine cells that secrete mucus into the lumen of the tract and endocrine cells that release hormones into the blood. Invaginations of the epithelium into the underlying tissue form exocrine glands that secrete acid, enzymes, water, and ions, as well as mucus.

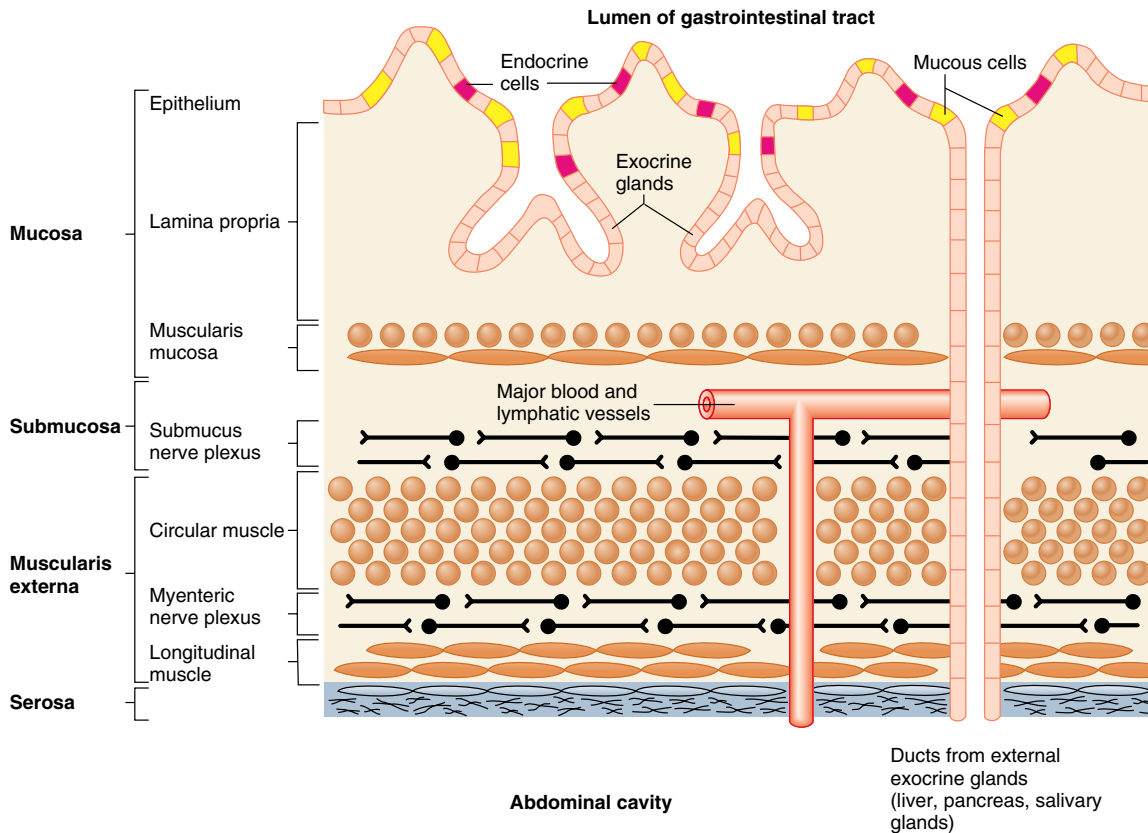
Just below the epithelium is a layer of connective tissue, the lamina propria, through which pass small blood vessels, nerve fibers, and lymphatic ducts. (These structures are not shown in Figure 17-6 but are in Figure 17-7.) The lamina propria is separated from underlying tissues by a thin layer of smooth muscle, the muscularis mucosa. The combination of these three layers—the epithelium, lamina propria, and muscularis mucosa—is called the **mucosa** (Figure 17-6).

Beneath the mucosa is a second connective tissue layer, the submucosa, containing a network of nerve cells, termed the **submucous plexus**, and blood and lymphatic vessels whose branches penetrate into both the overlying mucosa and the underlying layers of smooth muscle called the **muscularis externa**. Contractions of these muscles provide the forces for moving and mixing the gastrointestinal contents. The muscularis externa has two layers: (1) a relatively thick inner layer of **circular muscle**, whose fibers are oriented in a circular pattern around the tube such that contraction produces a narrowing of the lumen, and (2) a thinner outer layer of **longitudinal muscle**, whose contraction shortens the tube. Between these two muscle layers is a second network of nerve cells known as the **myenteric plexus**.

Finally, surrounding the outer surface of the tube is a thin layer of connective tissue called the **serosa**. Thin sheets of connective tissue connect the serosa to the abdominal wall, supporting the gastrointestinal tract in the abdominal cavity.

Extending from the luminal surface of the small intestine are fingerlike projections known as **villi** (Figure 17-7). The surface of each villus is covered with a layer of epithelial cells whose surface membranes form small projections called **microvilli** (also known collectively as the brush border) (Figure 17-8). The combination of folded mucosa, villi, and microvilli increases the small intestine's surface area about 600-fold over that of a flat-surfaced tube having the same length and diameter. The human small intestine's total surface area is about 300 m<sup>2</sup>, the area of a tennis court.

Epithelial surfaces in the gastrointestinal tract are continuously being replaced by new epithelial cells. In the small intestine, new cells arise by cell division from cells at the base of the villi. These cells differentiate as

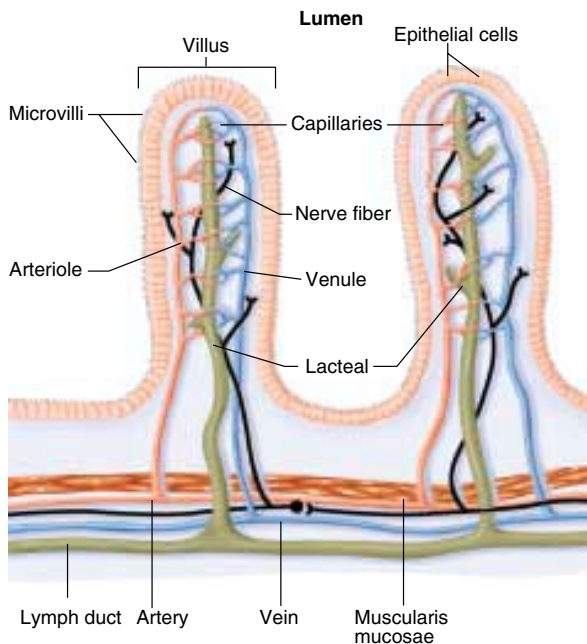


**FIGURE 17-6**

Structure of the gastrointestinal wall in longitudinal section. Not shown are the smaller blood vessels and lymphatics, neural connections between the two nerve plexuses, and neural terminations on muscles, glands and epithelium.

they migrate to the top of the villus, replacing older cells that disintegrate and are discharged into the intestinal lumen. These disintegrating cells release into the lumen their intracellular enzymes, which then contribute to the digestive process. About 17 billion epithelial cells are replaced each day, and the entire epithelium of the small intestine is replaced approximately every 5 days. It is because of this rapid cell turnover that the lining of the intestinal tract is so susceptible to damage by agents, such as radiation and anticancer drugs, that inhibit cell division.

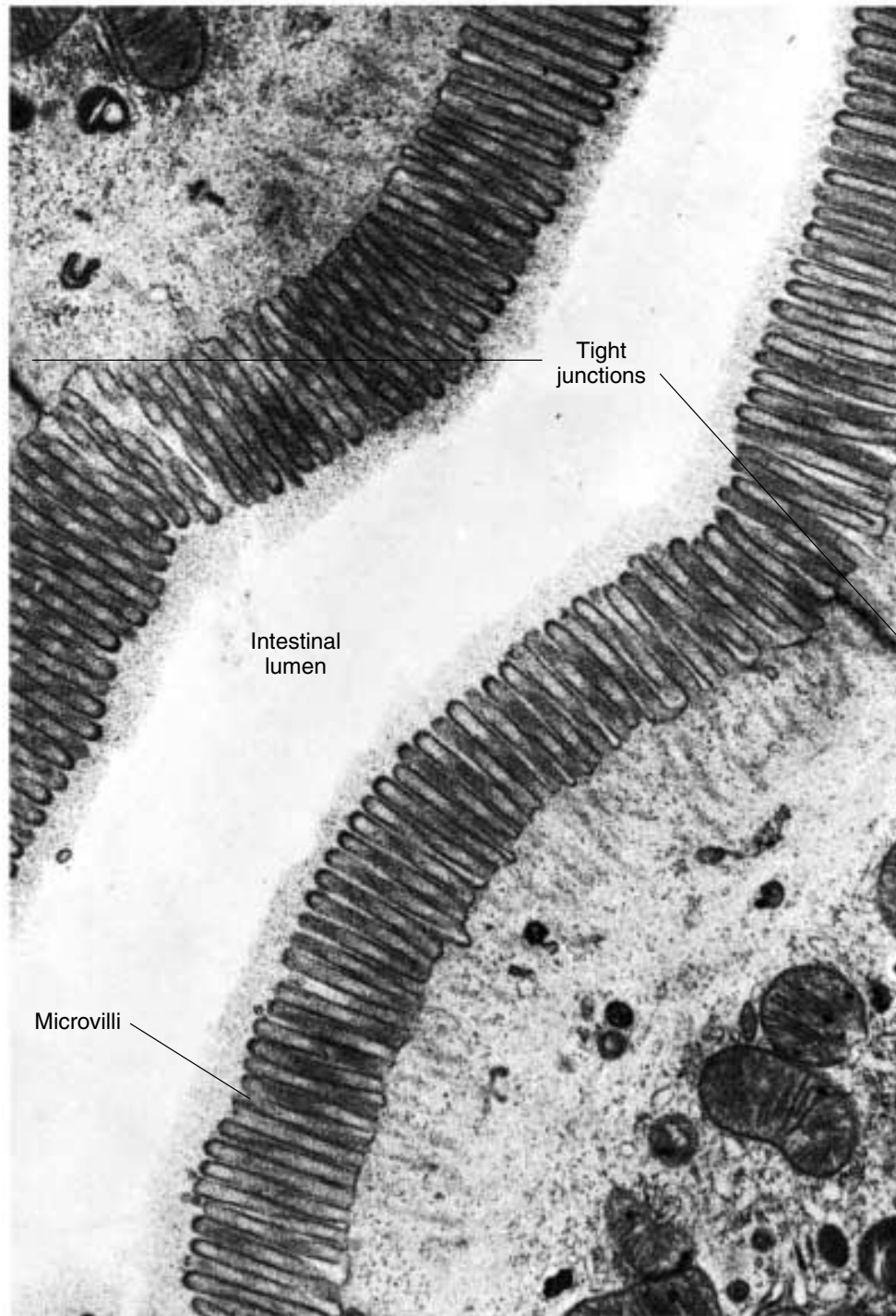
The center of each intestinal villus is occupied both by a single blind-ended lymphatic vessel termed a **lacteal** and by a capillary network (see Figure 17-7). As we will see, most of the fat absorbed in the small intestine enters the lacteals, while other absorbed nutrients enter the blood capillaries. The venous drainage from the small intestine, as well as from the large



**FIGURE 17-7**

Structure of villi in small intestine. ✎





**FIGURE 17-8**

Microvilli on the surface of intestinal epithelial cells.

From D. W. Fawcett, J. *Histochem. Cytochem.* 13: 75-91 (1965). Courtesy of Susumo Ito.

intestine, pancreas, and portions of the stomach, does not empty directly into the vena cava but passes first, via the **hepatic portal vein**, to the liver. There it flows through a second capillary network before leaving the liver to return to the heart. Thus, material absorbed into the intestinal capillaries, in contrast to the lacteals, can be processed by the liver before entering the general circulation.

## Digestion and Absorption

### Carbohydrate

Carbohydrate intake per day ranges from about 250 to 800 g in a typical American diet. About two-thirds of this carbohydrate is the plant polysaccharide starch, and most of the remainder consists of the disaccharides sucrose (table sugar) and lactose (milk sugar) (Table 17–2). Only small amounts of monosaccharides are normally present in the diet. Cellulose and certain other complex polysaccharides found in vegetable matter—referred to as **fiber**—cannot be broken down by the enzymes in the small intestine and are passed on to the large intestine, where they are partially metabolized by bacteria.

Starch digestion by salivary amylase begins in the mouth and continues in the upper part of the stomach before the amylase is destroyed by gastric acid. Starch digestion is completed in the small intestine by pancreatic amylase. The products produced by both amylases are the disaccharide maltose and a mixture of short, branched chains of glucose molecules. These products, along with ingested sucrose and lactose, are broken down into monosaccharides—glucose, galactose, and fructose—by enzymes located on the luminal membranes of the small-intestine epithelial cells. These monosaccharides are then transported across the intestinal epithelium into the blood. Fructose enters the epithelial cells by facilitated diffusion, while glucose and galactose undergo secondary active transport coupled to sodium. These monosaccharides then leave the epithelial cells and enter the blood by way of facilitated diffusion transporters in the basolateral membranes of the epithelial cells. Most ingested carbohydrate is digested and absorbed within the first 20 percent of the small intestine.

### Protein

Only 40 to 50 g of protein per day is required by a normal adult to supply essential amino acids and replace the amino acid nitrogen converted to urea. A typical American diet contains about 125 g of protein per day. In addition, a large amount of protein, in the form of enzymes and mucus, is secreted into the gastrointestinal tract or enters it via the disintegration of epithelial cells. Regardless of source, most of the protein in the

TABLE 17–2 Carbohydrates in Food

Class	Examples	Made of
Polysaccharides	Starch	Glucose
	Cellulose	Glucose
	Glycogen	Glucose
Disaccharides	Sucrose	Glucose-fructose
	Lactose	Glucose-galactose
	Maltose	Glucose-glucose
Monosaccharides	Glucose	
	Fructose	
	Galactose	

lumen is broken down into amino acids and absorbed by the small intestine.

Proteins are broken down to peptide fragments in the stomach by pepsin, and in the small intestine by **trypsin** and **chymotrypsin**, the major proteases secreted by the pancreas. These fragments are further digested to free amino acids by **carboxypeptidase** from the pancreas and **aminopeptidase**, located on the luminal membranes of the small-intestine epithelial cells. These last two enzymes split off amino acids from the carboxyl and amino ends of peptide chains, respectively. At least 20 different peptidases are located on the luminal membrane of the epithelial cells, with various specificities for the peptide bonds they attack.

The free amino acids then enter the epithelial cells by secondary active transport coupled to sodium. There are multiple transporters with different specificities for the 20 types of amino acids. Short chains of two or three amino acids are also absorbed by a secondary active transport that is coupled to the hydrogen gradient. (This is in contrast to carbohydrate absorption, in which molecules larger than monosaccharides are not absorbed.) Within the epithelial cell, these di- and tripeptides are hydrolyzed to amino acids, which then leave the cell and enter the blood through a facilitated diffusion carrier in the basolateral membranes. As with carbohydrates, protein digestion and absorption are largely completed in the upper portion of the small intestine.

Very small amounts of intact proteins are able to cross the intestinal epithelium and gain access to the interstitial fluid. They do so by a combination of endocytosis and exocytosis. The absorptive capacity for intact proteins is much greater in infants than in adults, and antibodies (proteins involved in the immunological defense system of the body) secreted into the mother's milk can be absorbed by the infant, providing some immunity until the infant begins to produce its own antibodies.

### Fat

Fat intake ranges from about 25 to 160 g/day in a typical American diet; most is in the form of triacylglycerols. Fat digestion occurs almost entirely in the small intestine. The major digestive enzyme in this process is pancreatic **lipase**, which catalyzes the splitting of bonds linking fatty acids to the first and third carbon atoms of glycerol, producing two free fatty acids and a monoglyceride as products:

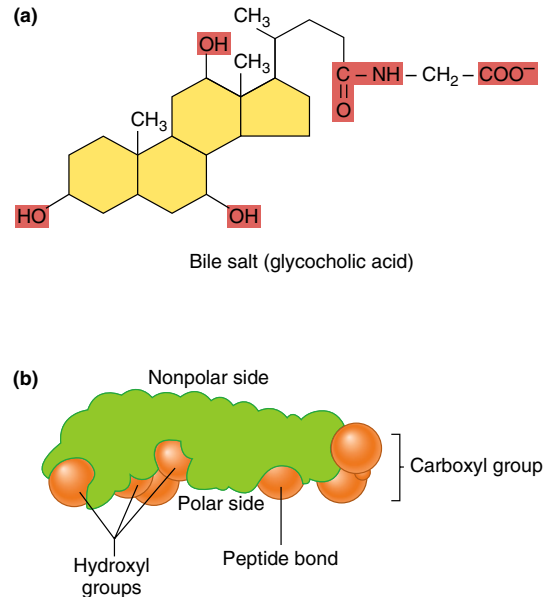


The fats in the ingested foods are insoluble in water and aggregate into large lipid droplets in the upper portion of the stomach. Since pancreatic lipase is a water-soluble enzyme, its digestive action in the small intestine can take place only at the *surface* of a lipid droplet. Therefore, if most of the ingested fat remained in large lipid droplets, the rate of lipid digestion would be very slow. The rate of digestion is, however, substantially increased by division of the large lipid droplets into a number of much smaller droplets, thereby increasing their surface area and accessibility to lipase action. This process is known as **emulsification**, and the resulting suspension of small lipid droplets is an emulsion.

The emulsification of fat requires (1) mechanical disruption of the large fat droplets into smaller droplets, and (2) an emulsifying agent, which acts to prevent the smaller droplets from reaggregating back into large droplets. The mechanical disruption is provided by contractile activity, occurring in the lower portion of the stomach and in the small intestine, which acts to grind and mix the luminal contents. Phospholipids in food and phospholipids and bile salts secreted in the bile provide the emulsifying agents, whose action is as follows.

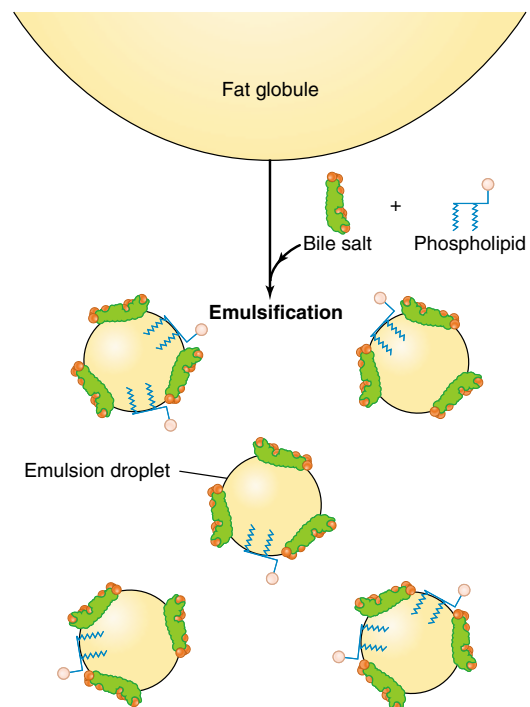
Phospholipids are amphipathic molecules (Chapter 2) consisting of two nonpolar fatty acid chains attached to glycerol, with a charged phosphate group located on glycerol's third carbon. Bile salts are formed from cholesterol in the liver and are also amphipathic (Figure 17-9). The nonpolar portions of the phospholipids and bile salts associate with the nonpolar interior of the lipid droplets, leaving the polar portions exposed at the water surface. There they repel other lipid droplets that are similarly coated with these emulsifying agents, thereby preventing their reaggregation into larger fat droplets (Figure 17-10).

The coating of the lipid droplets with these emulsifying agents, however, impairs the accessibility of the water-soluble lipase to its lipid substrate. To overcome this problem, the pancreas secretes a protein known as **colipase**, which is amphipathic and lodges on the lipid droplet surface. Colipase binds the lipase enzyme, holding it on the surface of the lipid droplet.



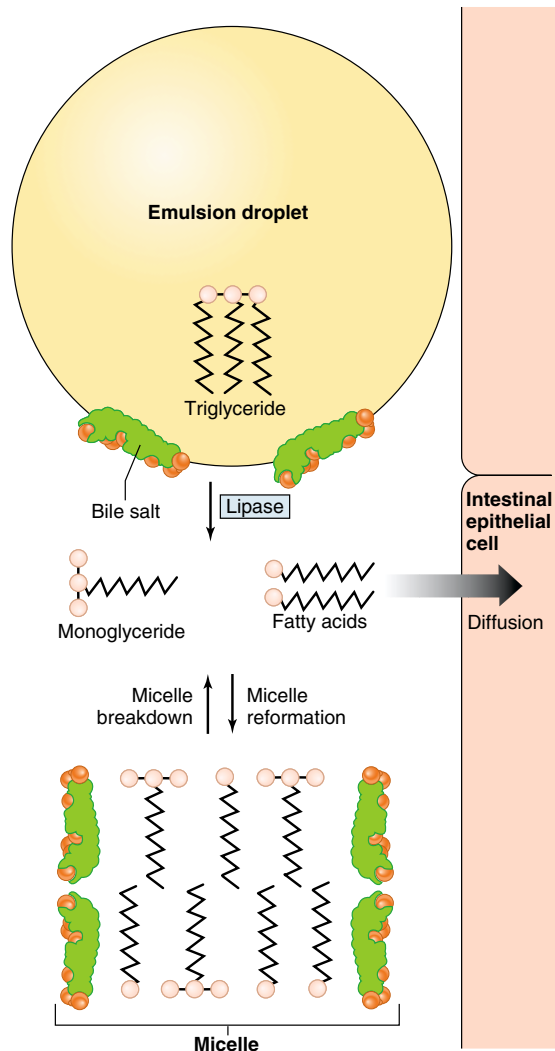
**FIGURE 17-9**

Structure of bile salts. (a) Chemical formula of glycocholic acid, one of several bile salts secreted by the liver (polar groups in color). (b) Three-dimensional structure of a bile salt, showing its polar and nonpolar surfaces.




**FIGURE 17-10**

Emulsification of fat by bile salts and phospholipids.



**FIGURE 17-11**

The products of fat digestion by lipase are held in solution in the micellar state, combined with bile salts and phospholipids. For simplicity, the phospholipids and colipase (see text) are not shown and the size of the micelle is greatly exaggerated. 

Although digestion is speeded up by emulsification, absorption of the water-insoluble products of the lipase reaction would still be very slow if it were not for a second action of the bile salts, the formation of **micelles**, which are similar in structure to emulsion droplets but are much smaller—4 to 7 nm in diameter. Micelles consist of bile salts, fatty acids, monoglycerides, and phospholipids all clustered together with the polar ends of each molecule oriented toward the micelle's surface and the nonpolar portions forming the micelle's core (Figure 17-11). Also included in

the core of the micelle are small amounts of fat-soluble vitamins and cholesterol.

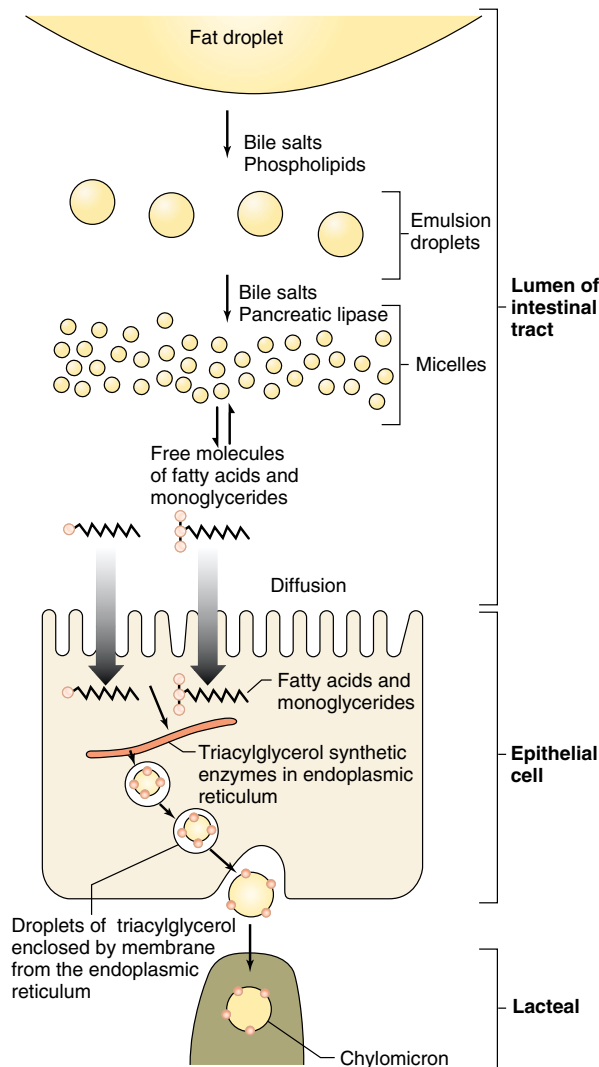
How do micelles increase absorption? Although fatty acids and monoglycerides have an extremely low solubility in water, a few molecules do exist in solution and are free to diffuse across the lipid portion of the luminal plasma membranes of the epithelial cells lining the small intestine. Micelles, containing the products of fat digestion, are in equilibrium with the small concentration of fat digestion products that are free in solution. Thus, micelles are continuously breaking down and reforming. When a micelle breaks down, its contents are released into the solution and become available to diffuse across the intestinal lining. As the concentrations of free lipids fall, because of their diffusion into epithelial cells, more lipids are released into the free phase as micelles break down (Figure 17-11). Thus, the micelles provide a means of keeping most of the insoluble fat digestion products in small soluble aggregates, while at the same time replenishing the small amount of products that are free in solution and are able to diffuse into the intestinal epithelium. Note that it is not the micelle that is absorbed but rather the individual lipid molecules that are released from the micelle.

Although fatty acids and monoglycerides enter epithelial cells from the intestinal lumen, it is triacylglycerol that is released on the other side of the cell into the interstitial fluid. In other words, during their passage through the epithelial cells, fatty acids and monoglycerides are resynthesized into triacylglycerols. This occurs in the agranular (smooth) endoplasmic reticulum, where the enzymes for triacylglycerol synthesis are located. This process lowers the concentration of cytosolic free fatty acids and monoglycerides and thus maintains a diffusion gradient for these molecules into the cell. Within this organelle, the resynthesized fat aggregates into small droplets coated with amphipathic proteins that perform an emulsifying function similar to that of bile salts.

The exit of these fat droplets from the cell follows the same pathway as a secreted protein. Vesicles containing the droplet pinch off the endoplasmic reticulum, are processed through the Golgi apparatus, and eventually fuse with the plasma membrane, releasing the fat droplet into the interstitial fluid. These one-micron-diameter, extracellular fat droplets are known as **chylomicrons**. Chylomicrons contain not only triacylglycerols but other lipids (including phospholipids, cholesterol, and fat-soluble vitamins) that have been absorbed by the same process that led to fatty acid and monoglyceride movement into the epithelial cells of the small intestine.

The chylomicrons released from the epithelial cells pass into lacteals—lymphatic capillaries in the





**FIGURE 17-12** Summary of fat absorption across the walls of the small intestine. ✎

intestinal villi—rather than into the blood capillaries. The chylomicrons cannot enter the blood capillaries because the basement membrane (an extracellular glycoprotein layer) at the outer surface of the capillary provides a barrier to the diffusion of large chylomicrons. In contrast, the lacteals do not have basement membranes and have large slit pores between their endothelial cells through which the chylomicrons can pass into the lymph. The lymph from the small intestine, as from everywhere else in the body, eventually empties into systemic veins. In Chapter 18 we describe how the lipids in the circulating blood chylomicrons are made available to the cells of the body.

Figure 17-12 summarizes the pathway taken by fat in moving from the intestinal lumen into the lymphatic system.

### Vitamins

The fat-soluble vitamins—A, D, E, and K—follow the pathway for fat absorption described in the previous section. They are solubilized in micelles; thus, any interference with the secretion of bile or the action of bile salts in the intestine decreases the absorption of the fat-soluble vitamins.

With one exception, water-soluble vitamins are absorbed by diffusion or mediated transport. The exception, vitamin B<sub>12</sub>, is a very large, charged molecule. In order to be absorbed, vitamin B<sub>12</sub> must first bind to a protein, known as **intrinsic factor**, secreted by the acid-secreting cells in the stomach. Intrinsic factor with bound vitamin B<sub>12</sub> then binds to specific sites on the epithelial cells in the lower portion of the ileum, where vitamin B<sub>12</sub> is absorbed by endocytosis. As described in Chapter 14, vitamin B<sub>12</sub> is required for erythrocyte formation, and deficiencies result in *pernicious anemia*. This form of anemia may occur when the stomach either has been removed (as, for example, to treat ulcers or gastric cancer) or fails to secrete intrinsic factor. Since the absorption of vitamin B<sub>12</sub> occurs in the lower part of the ileum, removal of this segment because of disease can also result in pernicious anemia.

### Water and Minerals

Water is the most abundant substance in chyme. Approximately 8000 ml of ingested and secreted water enters the small intestine each day, but only 1500 ml is passed on to the large intestine since 80 percent of the fluid is absorbed in the small intestine. Small amounts of water are absorbed in the stomach, but the stomach has a much smaller surface area available for diffusion and lacks the solute-absorbing mechanisms that create the osmotic gradients necessary for net water absorption. The epithelial membranes of the small intestine are very permeable to water, and net water diffusion occurs across the epithelium whenever a water-concentration difference is established by the active absorption of solutes. The mechanisms coupling solute and water absorption by epithelial cells were described in Chapter 6.

Sodium ions account for much of the actively transported solute because they constitute the most abundant solute in chyme. Sodium absorption is a primary active process, using the Na,K-ATPase pumps in a manner described in Chapter 6 and similar to that for renal tubular sodium and water reabsorption (Chapter 16). Chloride and bicarbonate ions are absorbed with the sodium ions and contribute another large fraction of the absorbed solute.



Other minerals present in smaller concentrations, such as potassium, magnesium, and calcium, are also absorbed, as are trace elements such as iron, zinc, and iodide. Consideration of the transport processes associated with each of these is beyond the scope of this book, and we shall briefly consider as an example the absorption of only one—iron. Calcium absorption and its regulation were described in Chapter 16.

**Iron** Only about 10 percent of ingested iron is absorbed into the blood each day. Iron ions are actively transported into intestinal epithelial cells, where most of them are incorporated into ferritin, the protein-iron complex that functions as an intracellular iron store (Chapter 14). The absorbed iron that does not bind to ferritin is released on the blood side where it circulates throughout the body bound to the plasma protein transferrin. Most of the iron bound to ferritin in the epithelial cells is released back into the intestinal lumen when the cells at the tips of the villi disintegrate, and it is excreted in the feces.

Iron absorption depends on the body's iron content. When body stores are ample, the increased concentration of free iron in the plasma and intestinal epithelial cells leads to an increased transcription of the gene encoding the ferritin protein and thus an increased synthesis of ferritin. This results in the increased binding of iron in the intestinal epithelial cells and a reduction in the amount of iron released into the blood. When the body stores drop, for example, when there is a loss of hemoglobin during hemorrhage, the production and hence the concentration of intestinal ferritin decreases; the amount of iron bound to ferritin decreases, thereby increasing the unbound iron released into the blood.

Once iron has entered the blood, the body has very little means of excreting it, and it accumulates in tissues. Although the control mechanisms for iron absorption just described tend to maintain the iron content of the body fairly constant, a very large ingestion of iron can overwhelm them, leading to an increased deposition of iron in tissues and producing toxic effects. This condition is termed **hemochromatosis**. Some people have genetically defective control mechanisms and therefore develop hemochromatosis even when iron ingestion is normal.

Iron absorption also depends on the type of food ingested because it binds to many negatively charged ions in food, which can retard its absorption. For example, iron in ingested liver is much more absorbable than iron in egg yolk since the latter contains phosphates that bind the iron to form an insoluble and unabsorbable complex.

The absorption of iron is typical of that of most trace metals in several respects: (1) Cellular storage

proteins and plasma carrier proteins are involved, and (2) the control of *absorption*, rather than urinary excretion, is the major mechanism for the homeostatic control of the body's content of the trace metal.

## Regulation of Gastrointestinal Processes

Unlike control systems that regulate variables in the internal environment, the control mechanisms of the gastrointestinal system regulate conditions in the lumen of the tract. With few exceptions, like those just discussed for iron and other trace metals, these control mechanisms are governed not by the nutritional state of the body, but rather by the volume and composition of the luminal contents.

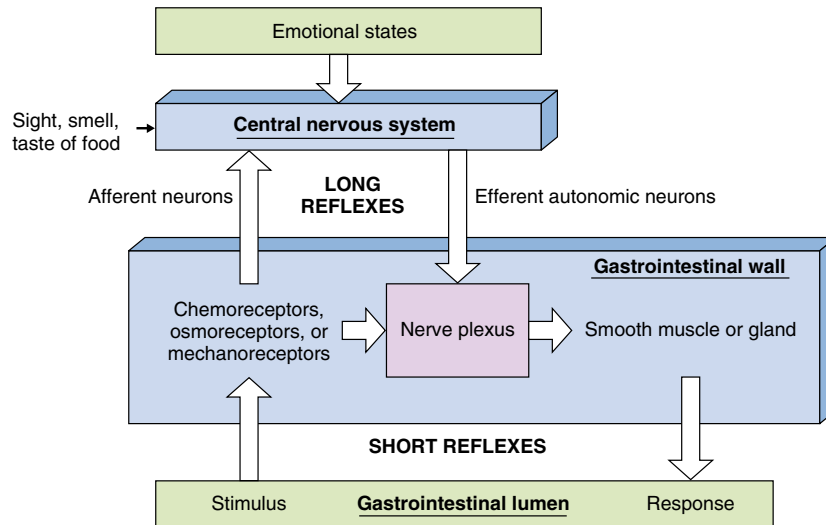
### Basic Principles

Gastrointestinal reflexes are initiated by a relatively small number of luminal stimuli: (1) distension of the wall by the volume of the luminal contents; (2) chyme osmolarity (total solute concentration); (3) chyme acidity; and (4) chyme concentrations of specific digestion products (monosaccharides, fatty acids, peptides, and amino acids). These stimuli act on receptors located in the wall of the tract (mechanoreceptors, osmoreceptors, and chemoreceptors) to trigger reflexes that influence the effectors—the muscle layers in the wall of the tract and the exocrine glands that secrete substances into its lumen.

**Neural Regulation** The gastrointestinal tract has its own local nervous system, known as the **enteric nervous system**, in the form of two nerve networks, the myenteric plexus and the submucous plexus (see Figure 17–6). These neurons either synapse with other neurons in the plexus or end near smooth muscles, glands, and epithelial cells. Many axons leave the myenteric plexus and synapse with neurons in the submucous plexus, and vice versa, so that neural activity in one plexus influences the activity in the other. Moreover, stimulation at one point in the plexus can lead to impulses that are conducted both up and down the tract. Thus, for example, stimuli in the upper part of the small intestine may affect smooth muscle and gland activity in the stomach as well as in the lower part of the intestinal tract.

The enteric nervous system contains adrenergic and cholinergic neurons as well as nonadrenergic, noncholinergic neurons that release neurotransmitters, such as nitric oxide, several neuropeptides, and ATP.

Many of the effectors mentioned earlier—muscle cells and exocrine glands—are supplied by neurons that are part of the enteric nervous system. This permits

**FIGURE 17-13**

Long and short neural reflex pathways activated by stimuli in the gastrointestinal tract. The long reflexes utilize neurons that link the central nervous system to the gastrointestinal tract.

neural reflexes that are completely within the tract—that is, independent of the central nervous system (CNS). In addition, nerve fibers from both the sympathetic and parasympathetic branches of the autonomic nervous system enter the intestinal tract and synapse with neurons in both plexuses. Via these pathways, the CNS can influence the motility and secretory activity of the gastrointestinal tract.

Thus, two types of neural reflex arcs exist (Figure 17-13): (1) **short reflexes** from receptors through the nerve plexuses to effector cells; and (2) **long reflexes** from receptors in the tract to the CNS by way of afferent nerves and back to the nerve plexuses and effector cells by way of autonomic nerve fibers. Some controls are mediated either solely by short reflexes or solely by long reflexes, whereas other controls involve both.

Finally, it should be noted that not all neural reflexes are indicated by signals *within* the tract. The sight or smell of food and the emotional state of an individual can have significant effects on the gastrointestinal tract, effects that are mediated by the CNS via autonomic neurons.

**Hormonal Regulation** The hormones that control the gastrointestinal system are secreted mainly by endocrine cells scattered throughout the epithelium of the stomach and small intestine; that is, these cells are not clustered into discrete organs like the thyroid or adrenal glands. One surface of each endocrine cell is exposed to the lumen of the gastrointestinal tract. At

this surface, various chemical substances in the chyme stimulate the cell to release its hormones from the opposite side of the cell into the blood. Although some of these hormones can also be detected in the lumen and may therefore act locally as paracrine agents, most of the gastrointestinal hormones reach their target cells via the circulation.

Several dozen substances are currently being investigated as possible gastrointestinal hormones, but only four—**secretin**, **cholecystokinin (CCK)**, **gastrin**, and **glucose-dependent insulinotropic peptide (GIP)**—have met all the criteria for true hormones. They, as well as several candidate hormones, also exist in the CNS and in gastrointestinal plexus neurons, where they function as neurotransmitters or neuromodulators.

Table 17-3, which summarizes the major characteristics of the four established GI hormones, not only serves as a reference for future discussions but also illustrates the following generalizations: (1) Each hormone participates in a feedback control system that regulates some aspect of the GI luminal environment, and (2) each hormone affects more than one type of target cell.

These two generalizations can be illustrated by CCK. The presence of fatty acids and amino acids in the small intestine triggers CCK secretion from cells in the small intestine into the blood. Circulating CCK then stimulates secretion by the pancreas of digestive enzymes. CCK also causes the gallbladder to contract, delivering to the intestine the bile salts required for micelle formation. As fat and amino acids are absorbed,

**TABLE 17–3 Properties of Gastrointestinal Hormones**

	Gastrin	CCK	Secretin	GIP
<b>Structure</b>	Peptide	Peptide	Peptide	Peptide
<b>Endocrine-Cell location</b>	Antrum of stomach	Small intestine	Small intestine	Small intestine
<b>Stimuli for hormone release</b>	Amino acids, peptides in stomach; parasympathetic nerves	Amino acids, fatty acids in small intestine	Acid in small intestine	Glucose, fat in small intestine
<b>Stimuli inhibiting hormone release</b>	Acid in stomach; somatostatin			

**Target-Cell Responses**

<b>Stomach</b>				
Acid secretion	Stimulates	Inhibits	Inhibits	
Motility	Stimulates	Inhibits	Inhibits	
Growth	Stimulates			
<b>Pancreas</b>				
Bicarbonate secretion		Potentiates secretin's actions	Stimulates	
Enzyme secretion		Stimulates	Potentiates CCK's actions	
Insulin secretion				Stimulates
Growth of exocrine pancreas	Stimulates	Stimulates	Stimulates	
<b>Liver (bile ducts)</b>				
Bicarbonate secretion		Potentiates secretin's actions	Stimulates	
<b>Gallbladder</b>				
Contraction		Stimulates		
<b>Sphincter of Oddi</b>				
		Relaxes		
<b>Small intestine</b>				
Motility	Stimulates ileum			
Growth	Stimulates			
<b>Large intestine</b>				
	Stimulates mass movement			

the stimuli (fatty acids and amino acids in the lumen) for CCK release are removed.

In many cases, a single effector cell contains receptors for more than one hormone, as well as receptors for neurotransmitters and paracrine agents, with the result that a variety of inputs can affect the cell's response. One such event is the phenomenon known as **potentiation**, which is exemplified by the interaction between secretin and CCK. Secretin strongly stimulates pancreatic bicarbonate secretion, whereas CCK is a weak stimulus of bicarbonate secretion. Both hormones together, however, stimulate pancreatic bicarbonate secretion more strongly than would be predicted by the sum of their individual stimulatory

effects. This is because CCK potentiates the effect of secretin. One of the consequences of potentiation is that small changes in the plasma concentration of one gastrointestinal hormone can have large effects on the actions of other gastrointestinal hormones.

In addition to their stimulation (or in some cases inhibition) of effector-cell functions, the gastrointestinal hormones also have tropic (growth-promoting) effects on various tissues, including the gastric and intestinal mucosa and the exocrine portions of the pancreas.

**Phases of Gastrointestinal Control** The neural and hormonal control of the gastrointestinal system is, in

large part, divisible into three phases—cephalic, gastric, and intestinal—according to stimulus location.

The **cephalic phase** is initiated when receptors in the head (*cephalic*, head) are stimulated by sight, smell, taste, and chewing. It is also initiated by various emotional states. The efferent pathways for these reflexes include both parasympathetic fibers, mostly in the vagus nerves, and sympathetic fibers. These fibers activate neurons in the gastrointestinal nerve plexuses, which in turn affect secretory and contractile activity.

Four types of stimuli in the stomach initiate the reflexes that constitute the **gastric phase** of regulation: distension, acidity, amino acids, and peptides formed during the digestion of ingested protein. The responses to these stimuli are mediated by short and long neural reflexes and by release of the hormone gastrin.

Finally, the **intestinal phase** is initiated by stimuli in the intestinal tract: distension, acidity, osmolarity, and various digestive products. The intestinal phase is mediated by both short and long neural reflexes and by the gastrointestinal hormones secretin, CCK, and GIP, all of which are secreted by endocrine cells in the small intestine.

We reemphasize that each of these phases is named for the site at which the various stimuli *initiate* the reflex and not for the sites of effector activity. Each phase is characterized by efferent output to virtually all organs in the gastrointestinal tract. Also, these phases do not occur in temporal sequence except at the very beginning of a meal. Rather, during ingestion and the much longer absorptive period, reflexes characteristic of all three phases may occur simultaneously.

Keeping in mind the neural and hormonal mechanisms available for regulating gastrointestinal activity, we can now examine the specific contractile and secretory processes that occur in each segment of the gastrointestinal system.

### **Mouth, Pharynx, and Esophagus**

**Chewing** Chewing is controlled by the somatic nerves to the skeletal muscles of the mouth and jaw. In addition to the voluntary control of these muscles, rhythmical chewing motions are reflexly activated by the pressure of food against the gums, hard palate at the roof of the mouth, and tongue. Activation of these mechanoreceptors leads to reflexive inhibition of the muscles holding the jaw closed. The resulting relaxation of the jaw reduces the pressure on the various mechanoreceptors, leading to a new cycle of contraction and relaxation.

Although chewing prolongs the subjective pleasure of taste, it does not appreciably alter the rate at which the food will be digested and absorbed. On the other hand, attempting to swallow a large particle of food can lead to choking if the particle lodges over the

trachea, blocking the entry of air into the lungs. A number of preventable deaths occur each year from choking, the symptoms of which are often confused with those of a heart attack so that no attempt is made to remove the obstruction from the airway. The Heimlich maneuver, described in Chapter 15, can often dislodge the obstructing particle from the airways.

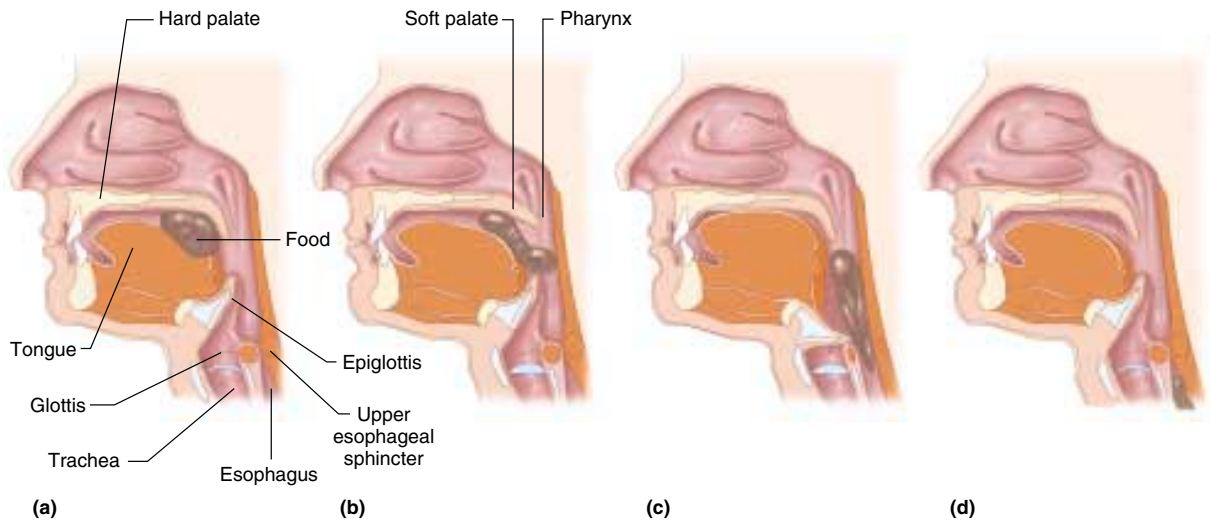
**Saliva** The secretion of saliva is controlled by both sympathetic and parasympathetic neurons; unlike their antagonistic activity in most organs, both systems stimulate salivary secretion, with the parasympathetics producing the greater response. There is no hormonal regulation of salivary secretion. In the absence of ingested material, a low rate of salivary secretion keeps the mouth moist. In the presence of food, salivary secretion increases markedly. This reflex response is initiated by chemoreceptors (acidic fruit juices are a particularly strong stimulus) and pressure receptors in the walls of the mouth and on the tongue.

Increased secretion of saliva is accomplished by a large increase in blood flow to the salivary glands, which is mediated by both neural activity and paracrine/autocrine agents released by the active cells in the salivary gland. The volume of saliva secreted per gram of tissue is the largest secretion of any of the body's exocrine glands.

**Swallowing** Swallowing is a complex reflex initiated when pressure receptors in the walls of the pharynx are stimulated by food or drink forced into the rear of the mouth by the tongue. These receptors send afferent impulses to the **swallowing center** in the brainstem medulla oblongata. This center then elicits swallowing via efferent fibers to the muscles in the pharynx and esophagus as well as to the respiratory muscles.

As the ingested material moves into the pharynx, the soft palate is elevated and lodges against the back wall of the pharynx, preventing food from entering the nasal cavity (Figure 17–14b). Impulses from the swallowing center inhibit respiration, raise the larynx, and close the **glottis** (the area around the vocal cords and the space between them), keeping food from moving into the trachea. As the tongue forces the food farther back into the pharynx, the food tilts a flap of tissue, the **epiglottis**, backward to cover the closed glottis (Figure 17–14c).

The next stage of swallowing occurs in the esophagus, the foot-long tube that passes through the thoracic cavity, penetrates the diaphragm, which separates the thoracic cavity from the abdominal cavity, and joins the stomach a few centimeters below the diaphragm. Skeletal muscles surround the upper third of the esophagus, smooth muscles the lower two-thirds.



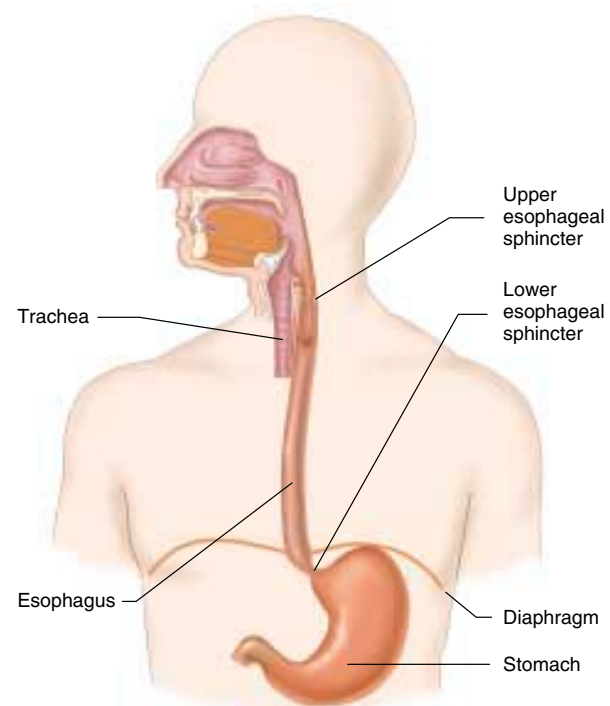
**FIGURE 17-14**

Movements of food through the pharynx and upper esophagus during swallowing. ⚡

As described in Chapter 15, the pressure in the thoracic cavity is 4 to 10 mmHg less than atmospheric pressure, and this subatmospheric pressure is transmitted across the thin wall of the intrathoracic portion of the esophagus to the lumen. In contrast, the luminal pressure in the pharynx at the opening to the esophagus is equal to atmospheric pressure, and the pressure at the opposite end of the esophagus in the stomach is slightly greater than atmospheric. Therefore, pressure differences exist that would tend to force both air (from above) and gastric contents (from below) into the esophagus. This does not occur, however, because both ends of the esophagus are normally closed by the contraction of sphincter muscles. Skeletal muscles surround the esophagus just below the pharynx and form the **upper esophageal sphincter**, whereas the smooth muscles in the last portion of the esophagus form the **lower esophageal sphincter** (Figure 17-15).

The esophageal phase of swallowing begins with relaxation of the upper esophageal sphincter. Immediately after the food has passed, the sphincter closes, and breathing resumes. Once in the esophagus, the food is moved toward the stomach by a progressive wave of muscle contractions that proceeds along the esophagus, compressing the lumen and forcing the food ahead of it. Such waves of contraction in the muscle layers surrounding a tube are known as **peristaltic waves**. One esophageal peristaltic wave takes about 9 s to reach the stomach. Swallowing can occur even when a person is upside down since it is not primarily gravity but the peristaltic wave that moves the food to the stomach.

The lower esophageal sphincter opens and remains relaxed throughout the period of swallowing, allowing the arriving food to enter the stomach. After the food has passed, the sphincter closes, resealing the junction between the esophagus and the stomach.



**FIGURE 17-15**

Location of upper and lower esophageal sphincters. ⚡



Swallowing is an example of a reflex in which multiple responses occur in a temporal sequence determined by the pattern of synaptic connections between neurons in a brain coordinating center. Since both skeletal and smooth muscles are involved, the swallowing center must direct efferent activity in both somatic nerves (to skeletal muscle) and autonomic nerves (to smooth muscle). Simultaneously, afferent fibers from receptors in the esophageal wall send information to the swallowing center that can alter the efferent activity. For example, if a large food particle does not reach the stomach during the initial peristaltic wave, the maintained distension of the esophagus by the particle activates receptors that initiate reflexes causing repeated waves of peristaltic activity (**secondary peristalsis**) that are not accompanied by the initial pharyngeal events of swallowing.

The ability of the lower esophageal sphincter to maintain a barrier between the stomach and the esophagus when swallowing is not taking place is aided by the fact that the last portion of the esophagus lies below the diaphragm, and is subject to the same abdominal pressures as is the stomach. In other words, if the pressure in the abdominal cavity is raised, for example, during cycles of respiration or by contraction of the abdominal muscles, the pressures on both the gastric contents and the terminal segment of the esophagus are raised together, preventing the formation of a pressure gradient between the stomach and esophagus that could force the stomach's contents into the esophagus.

During pregnancy the growth of the fetus not only increases the pressure on the abdominal contents but also pushes the terminal segment of the esophagus through the diaphragm into the thoracic cavity. The sphincter is therefore no longer assisted by changes in abdominal pressure. Accordingly, during the last half of pregnancy there is a tendency for increased abdominal pressure to force some of the gastric contents up into the esophagus. The hydrochloric acid from the stomach irritates the esophageal walls, producing pain known as **heartburn** (because the pain appears to be located over the heart). Heartburn often subsides in the last weeks of pregnancy as the uterus descends lower into the pelvis prior to delivery, decreasing the pressure on the stomach.

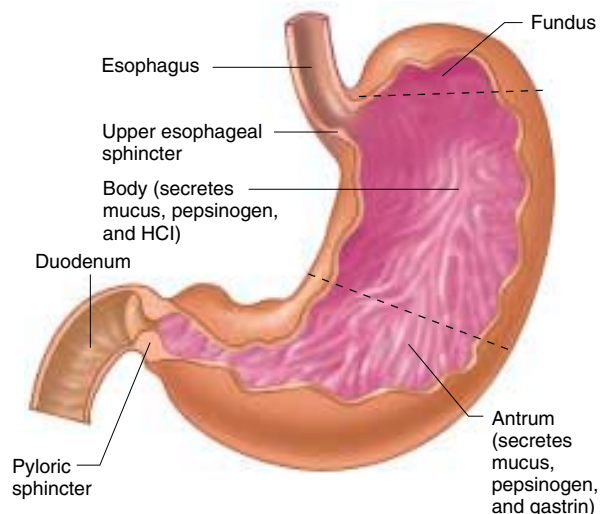
Heartburn also occurs in the absence of pregnancy. Some people have less efficient lower esophageal sphincters, resulting in repeated episodes of refluxed gastric contents into the esophagus (**gastro-esophageal reflux**), heartburn, and in extreme cases, ulceration, scarring, obstruction, or perforation of the lower esophagus. Heartburn can occur after a large meal, which can raise the pressure in the stomach enough to force acid into the esophagus. Gastro-esophageal reflux can also cause coughing and irritation of the larynx in the absence of any esophageal symptoms.

The lower esophageal sphincter not only undergoes brief periods of relaxation during a swallow but also in the absence of a swallow. During these periods of relaxation, small amounts of the acid contents from the stomach are normally refluxed into the esophagus. The acid in the esophagus triggers a secondary peristaltic wave and also stimulates increased salivary secretion, which helps to neutralize the acid and clear it from the esophagus.

### Stomach

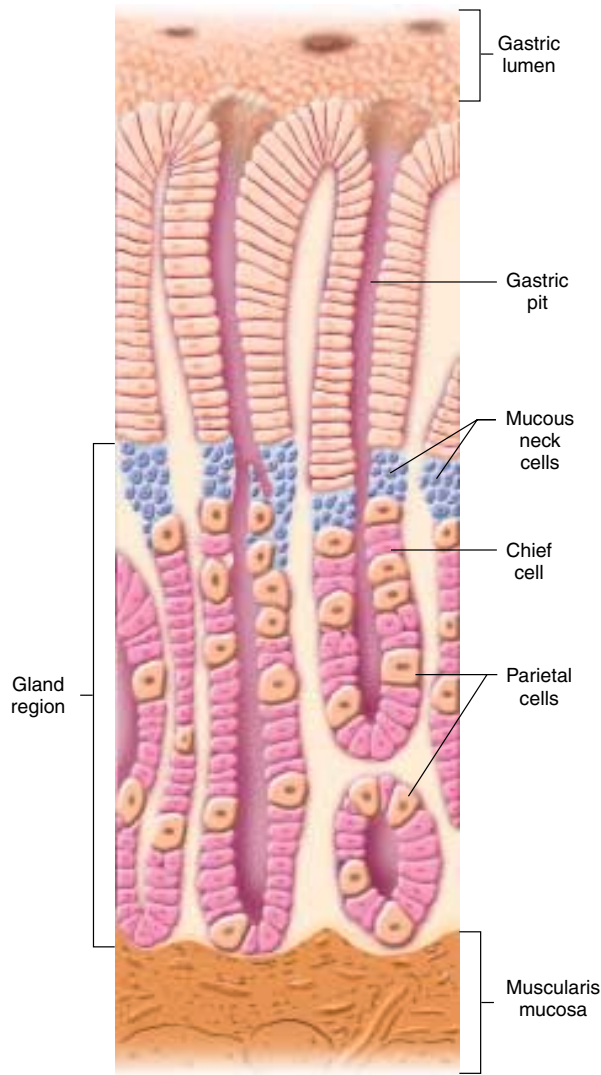
The epithelial layer lining the stomach invaginates into the mucosa, forming numerous tubular glands. Glands in the thin-walled upper portions of the stomach, the **body** and **fundus** (Figure 17–16), secrete mucus, hydrochloric acid, and the enzyme precursor **pepsinogen**. The lower portion of the stomach, the **antrum**, has a much thicker layer of smooth muscle. The glands in this region secrete little acid but contain the endocrine cells that secrete the hormone gastrin.

Mucus is secreted by the cells at the opening of the glands (Figure 17–17). Lining the walls of the glands are **parietal cells** (also known as oxyntic cells), which secrete acid and intrinsic factor, and **chief cells**, which secrete pepsinogen. Thus, each of the three major **exocrine** secretions of the stomach—mucus, acid, and pepsinogen—is secreted by a different cell type. In addition, **enterochromaffin-like (ECL) cells**, which release the paracrine agent histamine, and cells that secrete the peptide messenger somatostatin, are scattered throughout the tubular glands.



**FIGURE 17–16**

The three regions of the stomach: fundus, body, and antrum. ✂



**FIGURE 17-17**  
Gastric glands in the body of the stomach. ✂

**HCl Secretion** The stomach secretes about 2 L of hydrochloric acid per day. The concentration of hydrogen ions in the stomach's lumen may reach 150 mM, 3 million times greater than the concentration in the blood.

Primary H,K-ATPases in the luminal membrane of the parietal cells pump hydrogen ions into the stomach's lumen (Figure 17-18). This primary active transporter also pumps potassium into the cell, which then leaks back into the lumen through potassium channels. Excessive vomiting can lead to potassium depletion due to this leak. As hydrogen ions are secreted into the lumen, bicarbonate ions are being secreted on the

opposite side of the cell into the blood, in exchange for chloride ions. This addition of bicarbonate lowers the acidity in the venous blood from the stomach.

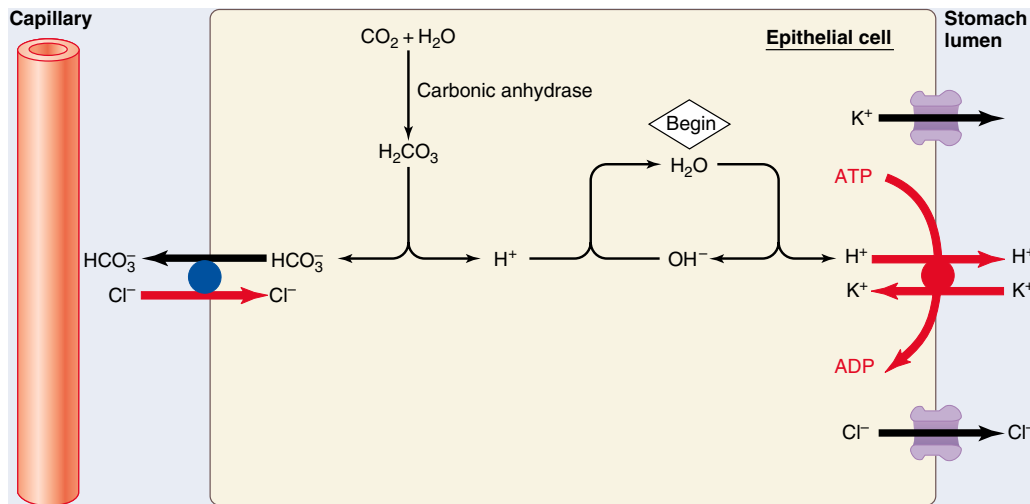
Increased acid secretion, stimulated by factors described in the next paragraph, is the result of the transfer of H,K-ATPase proteins from the membranes of intracellular vesicles to the plasma membrane by fusion of these vesicles with the membrane, thus increasing the number of pump proteins in the plasma membrane. This process is analogous to that described in Chapter 16 for the transfer of water channels to the plasma membrane of kidney collecting-duct cells in response to ADH.

Four chemical messengers regulate the insertion of H,K-ATPases into the plasma membrane and hence acid secretion: gastrin (a GI hormone), acetylcholine (ACh, a neurotransmitter), histamine, and somatostatin (two paracrine agents). Parietal cell membranes contain receptors for all four of these agents (Figure 17-19). Somatostatin inhibits acid secretion, while the other three stimulate secretion. Histamine is particularly important in stimulating acid secretion in that it markedly potentiates the response to the other two stimuli, gastrin and ACh. As will be discussed later when considering ulcers, this potentiating effect of histamine is the reason that drugs that block histamine receptors in the stomach suppress acid secretion. Not only do these chemical messengers act directly on the parietal cells, they also influence each other's secretion.

During a meal, the rate of acid secretion increases markedly as stimuli arising from the cephalic, gastric, and intestinal phases alter the release of the four chemical messengers described in the previous paragraph. During the cephalic phase, increased activity of the parasympathetic nerves to the stomach's enteric nervous system results in the release of ACh from the plexus neurons, gastrin from the gastrin-releasing cells, and histamine from ECL cells (Figure 17-20).

Once food has reached the stomach, the gastric phase stimuli—distension by the volume of ingested material and the presence of peptides and amino acids released by digestion of luminal proteins—produce a further increase in acid secretion. These stimuli use some of the same neural pathways used during the cephalic phase, in that nerve endings in the mucosa of the stomach respond to these luminal stimuli and send action potentials to the enteric nervous system, which in turn, can relay signals to the gastrin-releasing cells, histamine-releasing cells, and parietal cells. In addition, peptides and amino acids can act directly on the gastrin-releasing endocrine cells to promote gastrin secretion.

The concentration of acid in the gastric lumen is itself an important determinant of the rate of acid



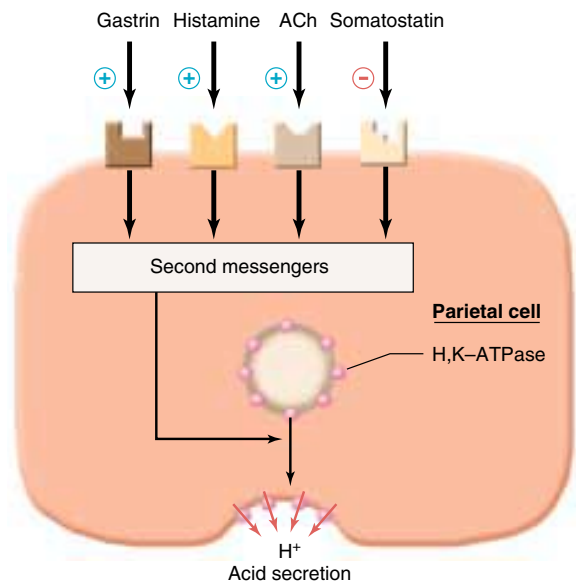
**FIGURE 17-18**

Secretion of hydrochloric acid by parietal cells. The hydrogen ions secreted into the lumen by primary active transport are derived from the breakdown of water molecules, leaving hydroxyl ions ( $\text{OH}^-$ ) behind. These hydroxyl ions are neutralized by combination with other hydrogen ions generated by the reaction between carbon dioxide and water, a reaction catalyzed by the enzyme carbonic anhydrase, which is present in high concentrations in parietal cells. The bicarbonate ions formed by this reaction move out of the parietal cell on the blood side, in exchange for chloride ions.

secretion for the following reason. Hydrogen ions (acid) stimulate the release of somatostatin from endocrine cells in the gastric wall. Somatostatin then acts on the parietal cells to inhibit acid secretion; it also inhibits the release of gastrin and histamine. The net result is a negative-feedback control of acid secretion; as the acidity of the gastric lumen increases, it turns off the stimuli that are promoting acid secretion.

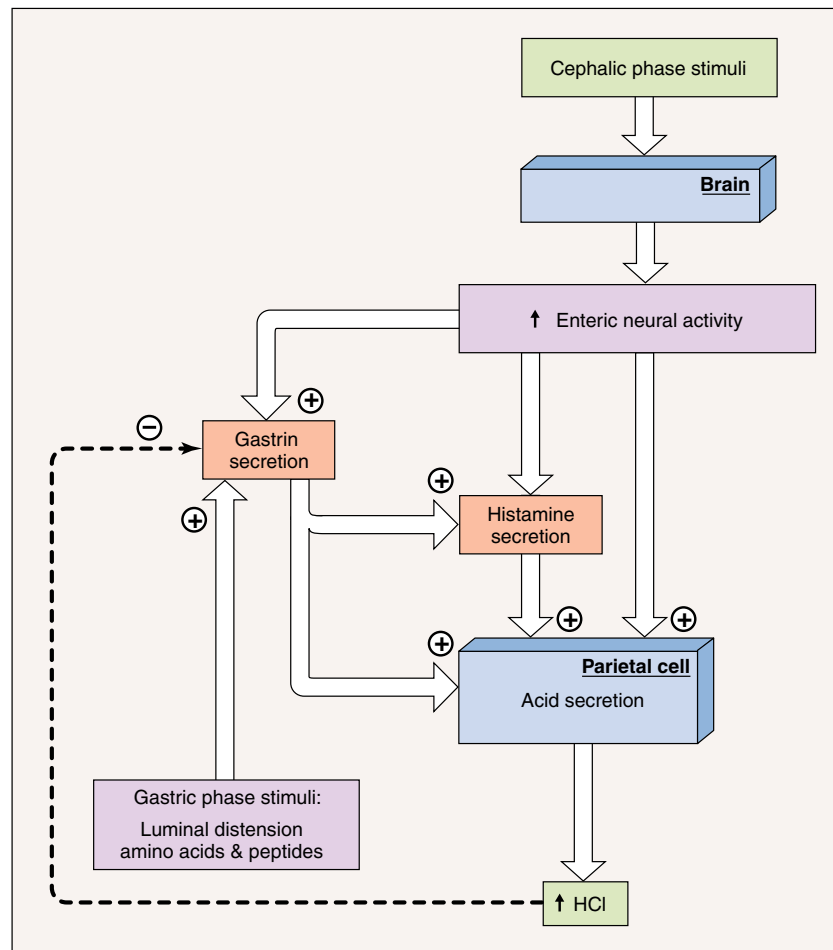
Increasing the protein content of a meal increases acid secretion. This occurs for two reasons. First, the more protein ingested, the more peptides are generated in the stomach's lumen, and these peptides, as we have seen, stimulate acid secretion. The second reason is more complicated and reflects the effects of proteins on luminal acidity. Before food enters the stomach, the  $\text{H}^+$  concentration in the lumen is *high* because there are few buffers present to bind any secreted hydrogen ions; therefore, the rate of acid secretion is *low* because high acidity inhibits acid secretion. The protein in food is an excellent buffer however, and so as protein enters the stomach the  $\text{H}^+$  concentration drops as the hydrogen ions bind to the proteins. This decrease in acidity removes the inhibition of acid secretion. The more protein in a meal, the greater the buffering of acid, and the more acid secreted.

We now come to the intestinal phase controlling acid secretion, the phase in which stimuli in the early



**FIGURE 17-19**

The four inputs to parietal cells that regulate acid secretion by controlling the transfer of the  $\text{H},\text{K}\text{-ATPase}$  pumps in cytoplasmic vesicle membranes to the plasma membrane.

**FIGURE 17–20**

Cephalic and gastric phases controlling acid secretion by the stomach.

portion of the *small intestine* influence acid secretion by the stomach. First, high acidity in the duodenum triggers reflexes that inhibit gastric acid secretion. This inhibition is beneficial for the following reason. The digestive activity of enzymes and bile salts in the small intestine is strongly inhibited by acidic solutions, and this reflex ensures that acid secretion by the stomach will be reduced whenever chyme entering the small intestine from the stomach contains so much acid that it cannot be rapidly neutralized by the bicarbonate-rich fluids simultaneously secreted into the intestine by the liver and pancreas.

Acid, distension, hypertonic solutions, and solutions containing amino acids, and fatty acids in the small intestine reflexly inhibit gastric acid secretion. Thus, the extent to which acid secretion is inhibited during the intestinal phase varies, depending upon the volume and composition of the intestinal contents, but the net result is the same—balancing the secretory ac-

tivity of the stomach with the digestive and absorptive capacities of the small intestine.

The inhibition of gastric acid secretion during the intestinal phase is mediated by short and long neural reflexes and by hormones that inhibit acid secretion by influencing the four signals *directly* controlling acid secretion: ACh, gastrin, histamine, and somatostatin. The hormones released by the intestinal tract that reflexly inhibit gastric activity are collectively called **enterogastrones** and include secretin, CCK, and additional unidentified hormones.

Table 17–4 summarizes the control of acid secretion.

**Pepsin Secretion** Pepsin is secreted by chief cells in the form of an inactive precursor called pepsinogen. The acidity in the stomach's lumen alters the shape of pepsinogen, exposing its active site so that this site can act on other pepsinogen molecules to break off a small chain of amino acids from their ends. This cleavage

**TABLE 17-4 Control of HCL Secretion during a Meal**

Stimuli	Pathways	Result
<b>Cephalic phase</b> Sight Smell Taste Chewing	Parasympathetic nerves to enteric nervous system	↑HCl secretion
<b>Gastric contents (gastric phase)</b> Distension ↑Peptides ↓H <sup>+</sup> concentration	Long and short neural reflexes, and direct stimulation of gastrin secretion	↑HCl secretion
<b>Intestinal contents (intestinal phase)</b> Distension ↑H <sup>+</sup> concentration ↑Osmolarity ↑Nutrient concentrations	Long and short neural reflexes; secretin, CCK, and other unspecified duodenal hormones	↓HCl secretion

converts pepsinogen to pepsin, the fully active form (Figure 17-21). Thus the activation of pepsin is an autocatalytic, positive-feedback process.

The synthesis and secretion of pepsinogen, followed by its intraluminal activation to pepsin, provides an example of a process that occurs with many other secreted proteolytic enzymes in the gastrointestinal tract. Because these enzymes are synthesized in inactive forms, collectively referred to as **zymogens**, any substrates that these enzymes might be able to act

upon *inside* the cell producing them are protected from digestion, thus preventing damage to the cells.

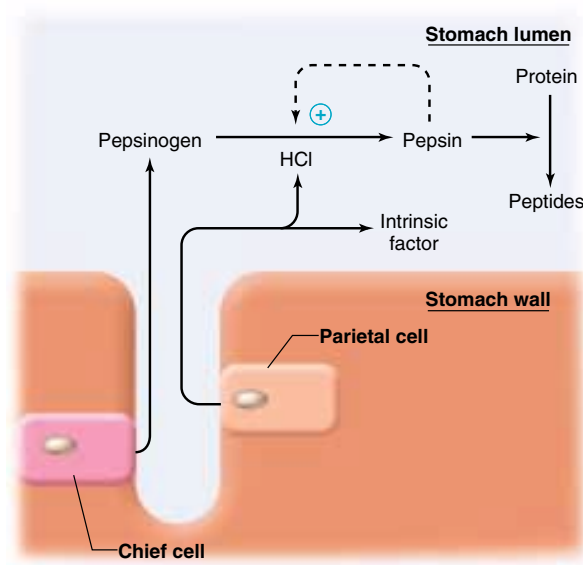
Pepsin is active only in the presence of a high H<sup>+</sup> concentration. It becomes inactive, therefore, when it enters the small intestine, where the hydrogen ions are neutralized by the bicarbonate ions secreted into the small intestine.

The primary pathway for stimulating pepsinogen secretion is input to the chief cells from the enteric nervous system. During the cephalic, gastric, and intestinal phases, most of the factors that stimulate or inhibit acid secretion exert the same effect on pepsinogen secretion. Thus, pepsinogen secretion parallels acid secretion.

Pepsin is not essential for protein digestion since in its absence, as occurs in some pathological conditions, protein can be completely digested by enzymes in the small intestine.

**Gastric Motility** An empty stomach has a volume of only about 50 ml, and the diameter of its lumen is only slightly larger than that of the small intestine. When a meal is swallowed, however, the smooth muscles in the fundus and body relax before the arrival of food, allowing the stomach's volume to increase to as much as 1.5 L with little increase in pressure. This is called **receptive relaxation** and is mediated by the parasympathetic nerves to the stomach's enteric nerve plexuses, with coordination by the swallowing center in the brain. Nitric oxide and serotonin released by enteric neurons mediate this relaxation.

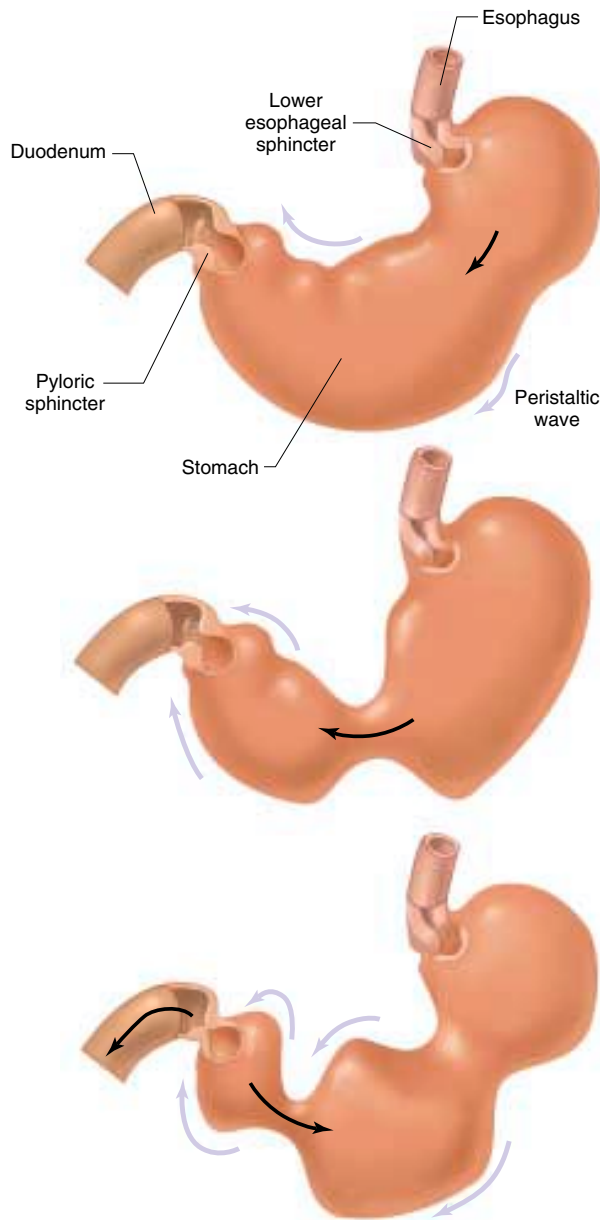
As in the esophagus, the stomach produces peristaltic waves in response to the arriving food. Each wave begins in the body of the stomach and produces only a ripple as it proceeds toward the antrum, a contraction




**FIGURE 17-21**

Conversion of pepsinogen to pepsin in the lumen of the stomach.





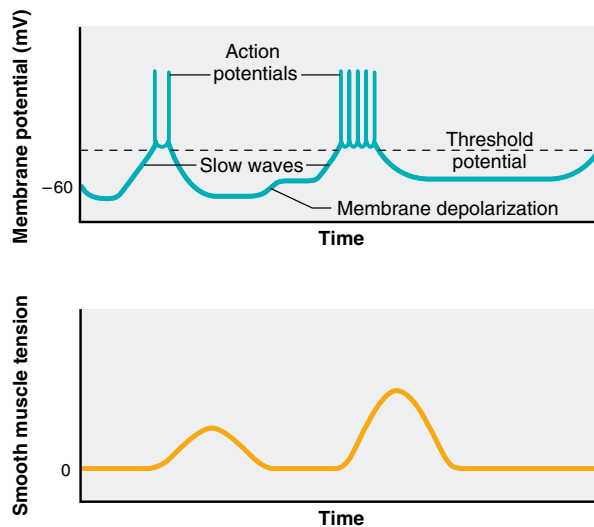
**FIGURE 17-22**

Peristaltic waves passing over the stomach force a small amount of luminal material into the duodenum. Black arrows indicate movement of luminal material; purple arrows indicate movement of the peristaltic wave in the stomach wall. 

too weak to produce much mixing of the luminal contents with acid and pepsin. As the wave approaches the larger mass of wall muscle surrounding the antrum, however, it produces a more powerful con-

traction, which both mixes the luminal contents and closes the **pyloric sphincter**, a ring of smooth muscle and connective tissue between the antrum and the duodenum (Figure 17-22). The pyloric sphincter muscles contract upon arrival of a peristaltic wave. As a consequence of sphincter closing, only a small amount of chyme is expelled into the duodenum with each wave, and most of the antral contents are forced backward toward the body of the stomach, thereby contributing to the mixing activity in the antrum.

What is responsible for producing gastric peristaltic waves? Their rhythm (three per minute) is generated by pacemaker cells in the longitudinal smooth muscle layer. These smooth-muscle cells undergo spontaneous depolarization-repolarization cycles (slow waves) known as the **basic electrical rhythm** of the stomach. These slow waves are conducted through gap junctions along the stomach's longitudinal muscle layer and also induce similar slow waves in the overlying circular muscle layer. In the absence of neural or hormonal input, however, these depolarizations are too small to cause significant contractions. Excitatory neurotransmitters and hormones act upon the smooth muscle to further depolarize the membrane, thereby bringing it closer to threshold. Action potentials may be generated at the peak of the slow wave cycle if threshold is reached (Figure 17-23) and thus cause



**FIGURE 17-23**

Slow wave oscillations in the membrane potential of gastric smooth-muscle fibers trigger bursts of action potentials when threshold potential is reached at the wave peak. Membrane depolarization brings the slow wave closer to threshold, increasing the action-potential frequency and thus the force of smooth-muscle contraction.

larger contractions. The number of spikes fired with each wave determines the strength of the muscle contraction.

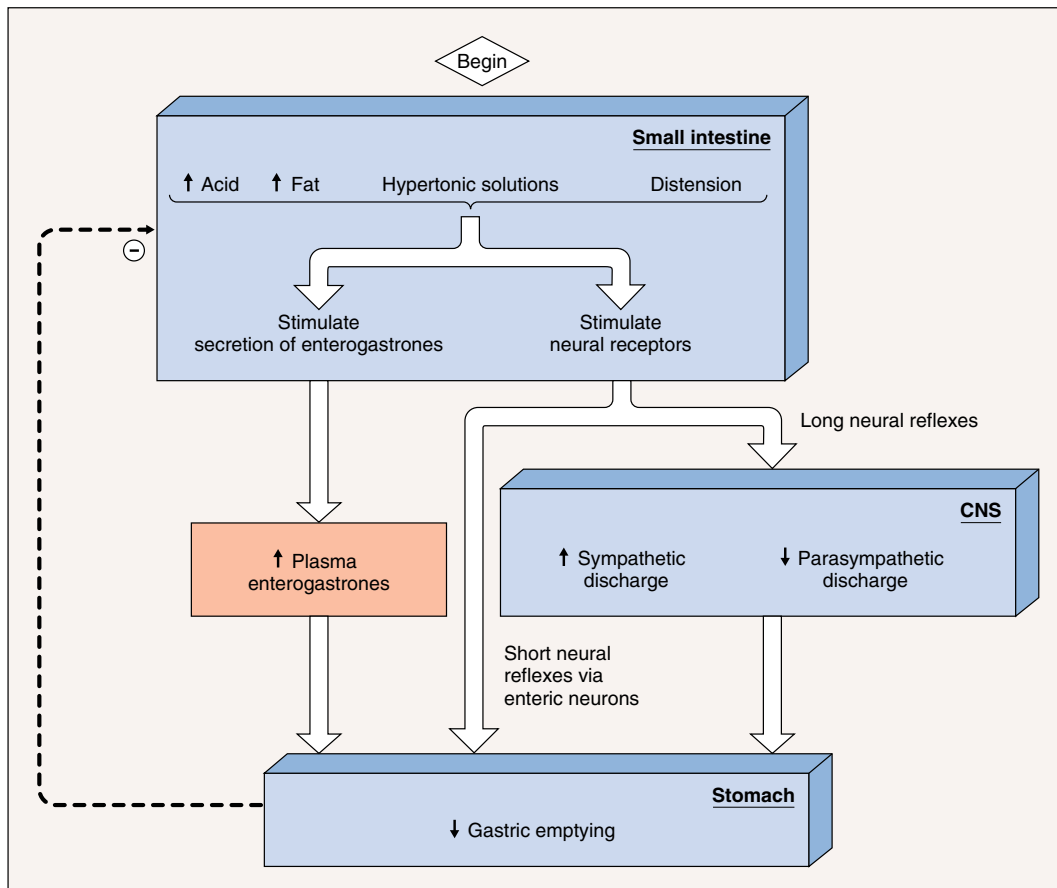
Thus, whereas the *frequency* of contraction is determined by the intrinsic basic electrical rhythm and remains essentially constant, the *force* of contraction and therefore the amount of gastric emptying per contraction are determined reflexly by neural and hormonal input to the antral smooth muscle.

The initiation of these reflexes depends upon the contents of both the stomach and small intestine. All the factors previously discussed that regulate acid secretion (Table 17–4) can also alter gastric motility. For example, gastrin, in sufficiently high concentrations, increases the force of antral smooth-muscle contractions. Distension of the stomach also increases the force of antral contractions through long and short reflexes triggered by mechanoreceptors in the stomach wall. Therefore, the larger a meal, the faster the stomach's initial emptying rate. As the volume of the stomach decreases, the force of gastric contractions and the rate of emptying also decrease.

In contrast, distension of the *duodenum* or the presence of fat, high acidity, or hypertonic solutions in its lumen all inhibit gastric emptying (Figure 17–24) just as they inhibit acid and pepsin secretion. Fat is the most potent of these chemical stimuli.

Autonomic nerve fibers to the stomach can be activated by the CNS independently of the reflexes originating in the stomach and duodenum and can influence gastric motility. Decreased parasympathetic or increased sympathetic activity inhibits motility. Via these pathways, pain and emotions such as sadness, depression, and fear tend to decrease motility, whereas aggression and anger tend to increase it. These relationships are not always predictable, however, and different people show different gastrointestinal responses to apparently similar emotional states.

As we have seen, a hypertonic solution in the duodenum is one of the stimuli inhibiting gastric emptying. This reflex prevents the fluid in the duodenum from becoming too hypertonic since it slows the rate of entry of chyme and thereby the delivery of large molecules that can rapidly be broken down into many



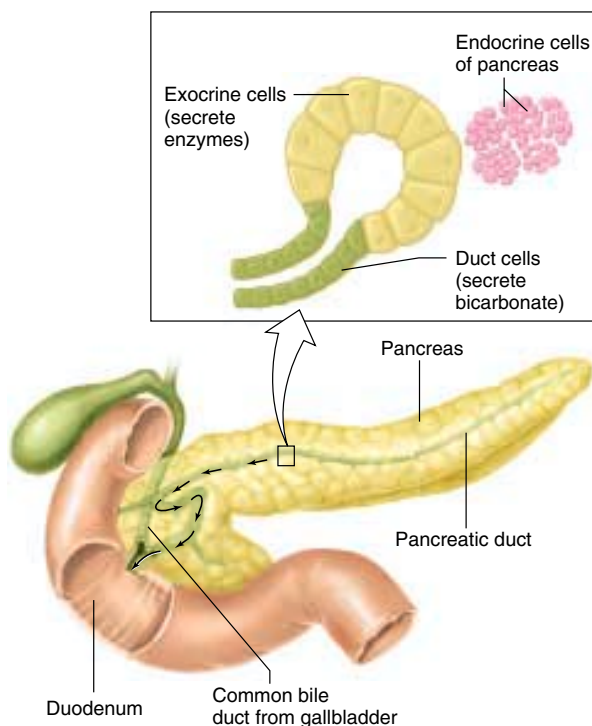
**FIGURE 17–24** Intestinal-phase pathways inhibiting gastric emptying.

small molecules by enzymes in the small intestine. A patient who has had his stomach removed because of disease (for example, cancer) must eat a number of small meals. A large meal, in the absence of the controlled emptying by the stomach, would rapidly enter the intestine, producing a hypertonic solution. This hypertonic solution can cause enough water to flow (by osmosis) into the intestine from the blood to lower the blood volume and produce circulatory complications. The large distension of the intestine by the entering fluid can also trigger vomiting in these patients. All these symptoms produced by the rapid entry of large quantities of ingested material into the small intestine are known as the *dumping syndrome*.

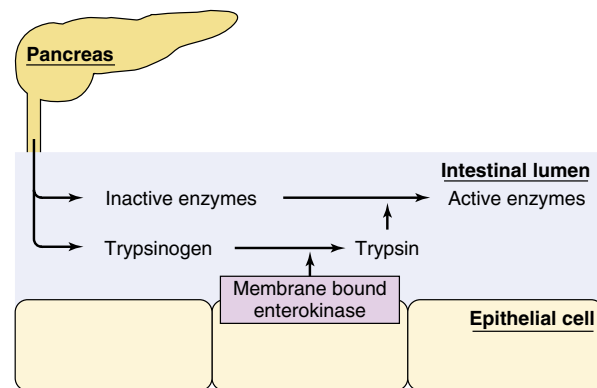
Once the contents of the stomach have emptied over a period of several hours, the peristaltic waves cease and the empty stomach is mostly quiescent. During this time, however, there are brief intervals of peristaltic activity that will be described along with the events controlling intestinal motility.

### Pancreatic Secretions

The exocrine portion of the pancreas secretes bicarbonate ions and a number of digestive enzymes into ducts that converge into the pancreatic duct, the latter joining the common bile duct from the liver just before this duct enters the duodenum (see Figure 17-4). The enzymes are secreted by gland cells at the pancreatic end of the



**FIGURE 17-25**  
Structure of the pancreas. ✎



**FIGURE 17-26**

Activation of pancreatic enzyme precursors in the small intestine.

duct system, whereas bicarbonate ions are secreted by the epithelial cells lining the ducts (Figure 17-25).

The mechanism of bicarbonate secretion is analogous to that of hydrochloric acid secretion by the stomach, except that the directions of hydrogen-ion and bicarbonate-ion movement are reversed. Hydrogen ions, derived from a carbonic anhydrase-catalyzed reaction between carbon dioxide and water, are actively transported out of the duct cells by an H-ATPase pump and released into the blood, while the bicarbonate ions are secreted into the duct lumen (see Figure 17-18).

The enzymes secreted by the pancreas digest fat, polysaccharides, proteins, and nucleic acids to fatty acids, sugars, amino acids, and nucleotides, respectively. A partial list of these enzymes and their activities is given in Table 17-5. The proteolytic enzymes are secreted in inactive forms (zymogens), as described for pepsinogen in the stomach, and then activated in the duodenum by other enzymes. A key step in this activation is mediated by **enterokinase**, which is embedded in the luminal plasma membranes of the intestinal epithelial cells. It is a proteolytic enzyme that splits off a peptide from pancreatic **trypsinogen**, forming the active enzyme trypsin. Trypsin is also a proteolytic enzyme, and once activated, it activates the other pancreatic zymogens by splitting off peptide fragments (Figure 17-26). This function is in addition to trypsin's role in digesting ingested protein.

The nonproteolytic enzymes secreted by the pancreas (for example, amylase) are released in fully active form. Along with lipase, the pancreas secretes colipase, whose function was described earlier.

Pancreatic secretion increases during a meal, mainly as a result of stimulation by the hormones secretin and CCK (see Table 17-3). Secretin is the primary stimulant for bicarbonate secretion, whereas CCK mainly stimulates enzyme secretion. (As noted earlier, these two hormones potentiate each other's actions.)

Since the function of pancreatic bicarbonate is to

**TABLE 17–5 Pancreatic Enzymes**

Enzyme	Substrate	Action
Trypsin, chymotrypsin, elastase	Proteins	Breaks peptide bonds in proteins to form peptide fragments
Carboxypeptidase	Proteins	Splits off terminal amino acid from carboxyl end of protein
Lipase	Fats	Splits off two fatty acids from triacylglycerols, forming free fatty acids and monoglycerides
Amylase	Polysaccharides	Splits polysaccharides into glucose and maltose
Ribonuclease, deoxyribonuclease	Nucleic acids	Splits nucleic acids into free mononucleotides

neutralize acid entering the duodenum from the stomach, it is appropriate that the major stimulus for secretin release is increased acidity in the duodenum (Figure 17–27). In analogous fashion, since CCK stimulates the secretion of digestive enzymes, including those for fat and protein digestion, it is appropriate that the stimuli for its release are fatty acids and amino acids in the duodenum (Figure 17–28).

Luminal acid and fatty acids also act on afferent nerve endings in the intestinal wall, initiating reflexes that act on the pancreas to increase both enzyme and bicarbonate secretion. Thus, the organic nutrients in the small intestine initiate, via hormonal and neural reflexes, the secretions involved in their own digestion.

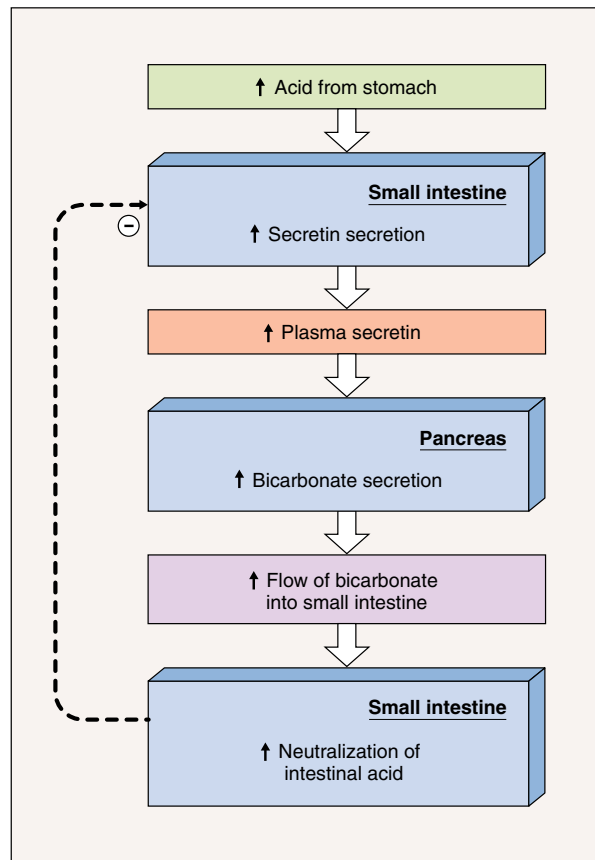
Although most of the pancreatic exocrine secretions are controlled by stimuli arising from the intestinal phase of digestion, cephalic and gastric stimuli, by way of the parasympathetic nerves to the pancreas, also play a role. Thus, the taste of food or the distension of the stomach by food, will lead to increased pancreatic secretion.

**Bile Secretion**

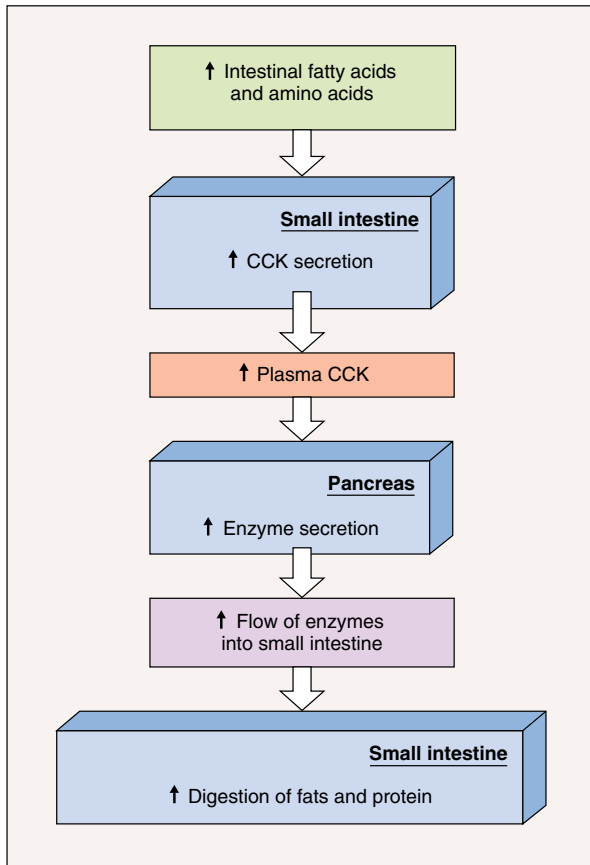
As stated earlier, bile is secreted by liver cells into a number of small ducts, the **bile canaliculi** (Figure 17–29), which converge to form the common hepatic duct (see Figure 17–4). Bile contains six major ingredients: (1) bile salts; (2) lecithin (a phospholipid); (3) bicarbonate ions and other salts; (4) cholesterol; (5) bile pigments and small amounts of other metabolic end products, and (6) trace metals. Bile salts and lecithin are synthesized in the liver and, as we have seen, help solubilize fat in the small intestine. Bicarbonate ions neutralize acid in the duodenum, and the last three ingredients represent substances extracted from the blood by the liver and excreted via the bile.

From the standpoint of gastrointestinal function, the most important components of bile are the bile

salts. During the digestion of a fatty meal, most of the bile salts entering the intestinal tract via the bile are absorbed by specific sodium-coupled transporters in



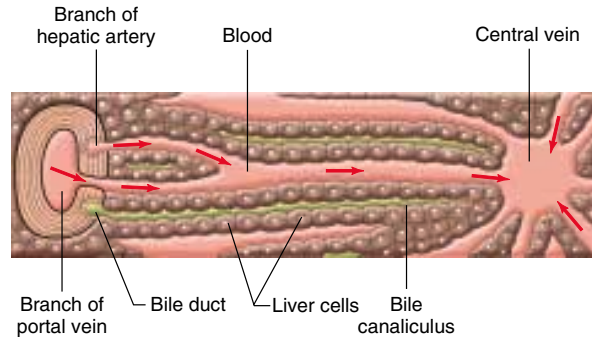
**FIGURE 17–27** Hormonal regulation of pancreatic bicarbonate secretion.



**FIGURE 17-28**  
Hormonal regulation of pancreatic enzyme secretion.

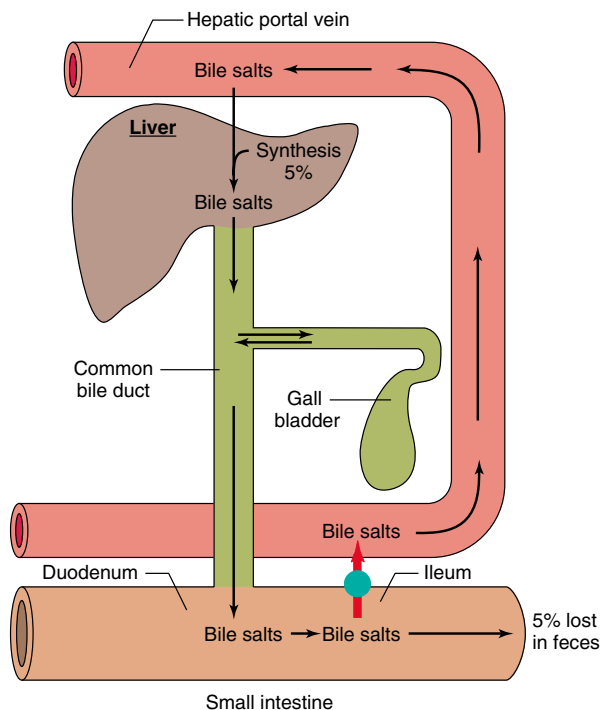
the ileum (the last segment of the small intestine). The absorbed bile salts are returned via the portal vein to the liver, where they are once again secreted into the bile. This recycling pathway from the intestine to the liver and back to the intestine is known as the **enterohepatic circulation** (Figure 17-30). A small amount (5 percent) of the bile salts escape this recycling and is lost in the feces, but the liver synthesizes new bile salts from cholesterol to replace them. During the digestion of a meal the entire bile salt content of the body may be recycled several times via the enterohepatic circulation.

In addition to synthesizing bile salts from cholesterol, the liver also secretes cholesterol extracted from the blood into the bile. Bile secretion, followed by excretion of cholesterol in the feces, is one of the mechanisms by which cholesterol homeostasis in the blood is maintained (Chapter 18). Cholesterol is insoluble in water, and its solubility in bile is achieved by its incorporation into micelles (whereas in the blood, cholesterol is incorporated into lipoproteins). Gallstones, consisting of precipitated cholesterol, will be discussed at the end of this chapter.



**FIGURE 17-29**  
A small section of the liver showing location of bile canaliculi and ducts with respect to blood and liver cells.  
Adapted from Kappas and Alvares.

**Bile pigments** are substances formed from the heme portion of hemoglobin when old or damaged erythrocytes are digested in the spleen and liver. The predominant bile pigment is **bilirubin**, which is extracted from the blood by liver cells and actively secreted into the bile. It is bilirubin that gives bile its yellow color. After entering the intestinal tract, bilirubin is modified by bacterial enzymes to form the brown



**FIGURE 17-30**  
Enterohepatic circulation of bile salts.



pigments that give feces their characteristic color. During their passage through the intestinal tract, some of the bile pigments are absorbed into the blood and are eventually excreted in the urine, giving urine its yellow color.

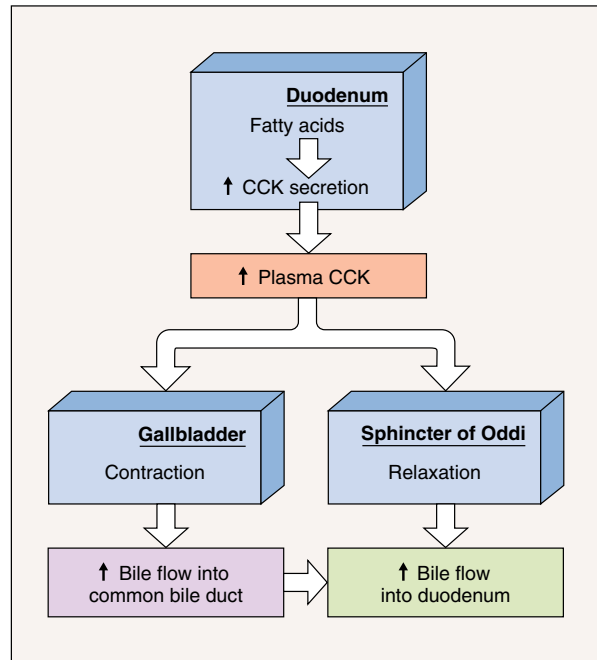
Like pancreatic secretions, the components of bile are secreted by two different cell types. The bile salts, cholesterol, lecithin, and bile pigments are secreted by **hepatocytes** (liver cells), whereas most of the bicarbonate-rich salt solution is secreted by the epithelial cells lining the bile ducts. Secretion of the salt solution by the bile ducts, just like that secreted by the pancreas, is stimulated by secretin in response to the presence of acid in the duodenum.

Unlike the pancreas, whose secretions are controlled by intestinal hormones, bile salt secretion is controlled by the concentration of bile salts in the blood—the greater the plasma concentration of bile salts, the greater their secretion into the bile canaliculi. Absorption of bile salts from the intestine during the digestion of a meal leads to their increased plasma concentration and thus to an increased rate of bile salt secretion by the liver. Although bile secretion is greatest during and just after a meal, some bile is always being secreted by the liver. Surrounding the common bile duct at the point where it enters the duodenum is a ring of smooth muscle known as the **sphincter of Oddi**. When this sphincter is closed, the dilute bile secreted by the liver is shunted into the gallbladder where the organic components of bile become concentrated as NaCl and water are absorbed into the blood.

Shortly after the beginning of a fatty meal, the sphincter of Oddi relaxes and the gallbladder contracts, discharging concentrated bile into the duodenum. The signal for gallbladder contraction and sphincter relaxation is the intestinal hormone CCK—appropriately so, since as we have seen, a major stimulus for this hormone's release is the presence of fat in the duodenum. (It is from this ability to cause contraction of the gallbladder that cholecystokinin received its name: *chole*, bile; *cysto*, bladder; *kinin*, to move). Figure 17–31 summarizes the factors controlling the entry of bile into the small intestine.

### Small Intestine

**Secretion** Approximately 1500 ml of fluid is secreted by the walls of the small intestine from the blood into the lumen each day. One of the reasons for water movement into the lumen (secretion) is that the intestinal epithelium at the base of the villi secretes a number of mineral ions, notably sodium, chloride, and bicarbonate ions into the lumen, and water follows by osmosis. These secretions, along with mucus, lubricate the surface of the intestinal tract and help protect the epithelial cells from excessive damage by the digestive



**FIGURE 17–31**

Regulation of bile entry into the small intestine.

enzymes in the lumen. Some damage to these cells still occurs, however, and the intestinal epithelium has one of the highest cell renewal rates of any tissue in the body.

Chloride is the primary ion determining the magnitude of fluid secretion. It exits the luminal membrane through the same chloride channel that is mutated in cystic fibrosis (Chapter 6). Various hormonal and paracrine signals—as well as certain bacterial toxins—can increase the opening frequency of these channels and thus increase fluid secretion.

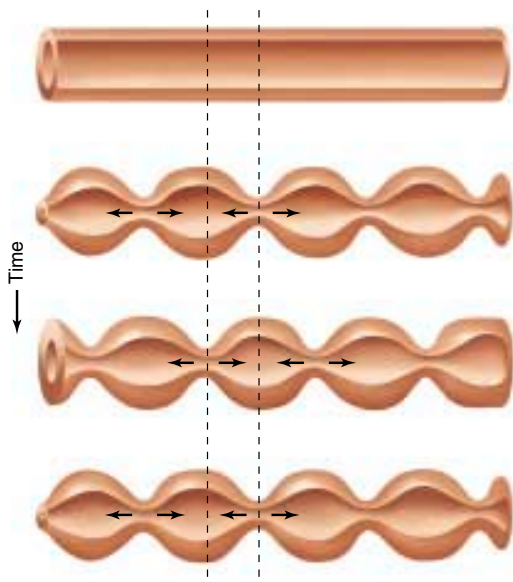
As stated earlier, water movement into the lumen also occurs when the chyme entering the small intestine from the stomach is hypertonic because of a high concentration of solutes in the meal and because digestion breaks down large molecules into many more small molecules. This hypertonicity causes the osmotic movement of water from the isotonic plasma into the intestinal lumen.

**Absorption** Normally, virtually all of the fluid secreted by the small intestine is absorbed back into the blood. In addition, a much larger volume of fluid, which includes salivary, gastric, hepatic, and pancreatic secretions, as well as ingested water, is simultaneously absorbed from the intestinal lumen into the blood. Thus, overall there is a large net absorption of water from the small intestine. Absorption is achieved


by the transport of ions, primarily sodium, from the intestinal lumen into the blood, with water following by osmosis.

The secretory and absorptive capacities of the intestinal epithelial cells become altered as newly derived cells at the base of the villi migrate to the tip. Cells at the base of the villi secrete fluid, while the older cells near the tip absorb fluid.

**Motility** In contrast to the peristaltic waves that sweep over the stomach, the most common motion in the small intestine during digestion of a meal is a stationary contraction and relaxation of intestinal segments, with little apparent net movement toward the large intestine (Figure 17–32). Each contracting segment is only a few centimeters long, and the contraction lasts a few seconds. The chyme in the lumen of a contracting segment is forced both up and down the intestine. This rhythmical contraction and relaxation of the intestine, known as **segmentation**, produces a continuous division and subdivision of the intestinal contents, thoroughly mixing the chyme in the lumen and bringing it into contact with the intestinal wall.



**FIGURE 17–32**

Segmentation movements of the small intestine in which segments of the intestine contract and relax in a rhythmical pattern but do not undergo peristalsis. This is the pattern encountered during a meal, which mixes the luminal contents. 

These segmenting movements are initiated by electrical activity generated by pacemaker cells in or associated with the circular smooth-muscle layer. Like the slow waves in the stomach, this intestinal basic electrical rhythm produces oscillations in the smooth-muscle membrane potential that, if threshold is reached, trigger action potentials that increase muscle contraction. The frequency of segmentation is set by the frequency of the intestinal basic electrical rhythm, but unlike the stomach, which normally has a single rhythm (three per minute), the intestinal rhythm varies along the length of the intestine, each successive region having a slightly lower frequency than the one above. For example, segmentation in the duodenum occurs at a frequency of about 12 contractions/min, whereas in the last portion of the ileum the rate is only 9 contractions/min. Segmentation produces, therefore, a slow migration of the intestinal contents toward the large intestine because more chyme is forced downward, on the average, than upward.

The intensity of segmentation can be altered by hormones, the enteric nervous system, and autonomic nerves; parasympathetic activity increases the force of contraction, and sympathetic stimulation decreases it. Thus, cephalic phase stimuli, including emotional states, can alter intestinal motility. As is true for the stomach, these inputs produce changes in the force of smooth-muscle contraction but do not significantly change the frequencies of the basic electrical rhythms.

After most of a meal has been absorbed, the segmenting contractions cease and are replaced by a pattern of peristaltic activity known as the **migrating motility complex**. Beginning in the lower portion of the stomach, repeated waves of peristaltic activity travel about 2 ft along the small intestine and then die out. This short segment of peristaltic activity slowly migrates down the small intestine, taking about 2 h to reach the large intestine. By the time the migrating motility complex reaches the end of the ileum, new waves are beginning in the stomach, and the process is repeated.

The migrating motility complex moves any undigested material still remaining in the small intestine into the large intestine and also prevents bacteria from remaining in the small intestine long enough to grow and multiply excessively. In diseases in which there is an aberrant migrating motility complex, bacterial overgrowth in the small intestine can become a major problem. Upon the arrival of a meal in the stomach, the migrating motility complex rapidly ceases in the intestine and is replaced by segmentation.

A rise in the plasma concentration of a candidate intestinal hormone, **motilin**, is thought to initiate the migrating motility complex. The mechanisms of motilin action and the control of its release have not been determined.

The contractile activity in various regions of the small intestine can be altered by reflexes initiated at different points along the gastrointestinal tract. For example, segmentation intensity in the ileum increases during periods of gastric emptying, and this is known as the **gastroileal reflex**. Large distensions of the intestine, injury to the intestinal wall, and various bacterial infections in the intestine lead to a complete cessation of motility, the **intestino-intestinal reflex**.

As much as 500 ml of air may be swallowed during a meal. Most of this air travels no farther than the esophagus, from which it is eventually expelled by belching. Some of the air reaches the stomach, however, and is passed on to the intestines, where its percolation through the chyme as the intestinal contents are mixed produces gurgling sounds that are often quite loud.

### Large Intestine

The large intestine is a tube 2.5 in. in diameter and about 4 ft long. Its first portion, the **cecum**, forms a blind-ended pouch from which extends the **appendix**, a small fingerlike projection having no known essential function (Figure 17–33). The **colon** consists of three relatively straight segments—the ascending, transverse, and descending portions. The terminal portion of the descending colon is S-shaped, forming the sigmoid colon, which empties into a relatively straight segment of the large intestine, the rectum, which ends at the anus.

Although the large intestine has a greater diameter than the small intestine, its epithelial surface area is far less, since the large intestine is about half as long as the small intestine, its surface is not convoluted, and

its mucosa lacks villi. The secretions of the large intestine are scanty, lack digestive enzymes, and consist mostly of mucus and fluid containing bicarbonate and potassium ions. The primary function of the large intestine is to store and concentrate fecal material before defecation.

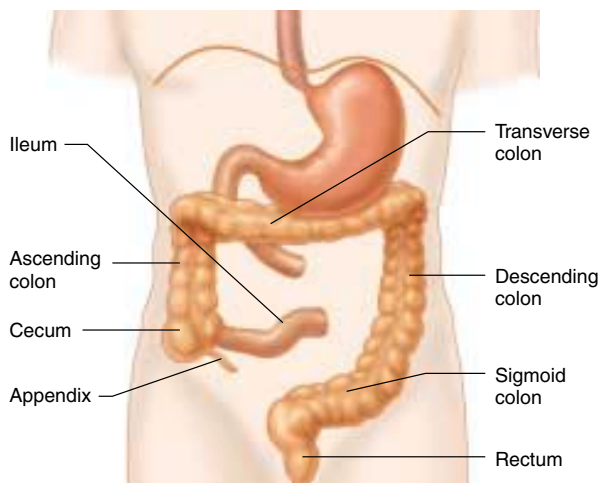
Chyme enters the cecum through the **ileocecal sphincter**. This sphincter is normally closed, but after a meal, when the gastroileal reflex increases ileal contractions, it relaxes each time the terminal portion of the ileum contracts, allowing chyme to enter the large intestine. Distension of the large intestine, on the other hand, produces a reflex contraction of the sphincter, preventing fecal material from moving back into the small intestine.

About 1500 ml of chyme enters the large intestine from the small intestine each day. This material is derived largely from the secretions of the lower small intestine since most of the ingested food has been absorbed before reaching the large intestine. Fluid absorption by the large intestine normally accounts for only a small fraction of the fluid entering the gastrointestinal tract each day.

The primary absorptive process in the large intestine is the active transport of sodium from lumen to blood, with the accompanying osmotic absorption of water. If fecal material remains in the large intestine for a long time, almost all the water is absorbed, leaving behind hard fecal pellets. There is normally a net movement of potassium from blood into the large-intestine lumen, and severe depletion of total-body potassium can result when large volumes of fluid are excreted in the feces. There is also a net movement of bicarbonate ions into the lumen, and loss of this bicarbonate (a base) in patients with prolonged diarrhea can cause the blood to become acidic.

The large intestine also absorbs some of the products formed by the bacteria inhabiting this region. Undigested polysaccharides (fiber) are metabolized to short-chain fatty acids by bacteria in the large intestine and absorbed by passive diffusion. The bicarbonate secreted by the large intestine helps to neutralize the increased acidity resulting from the formation of these fatty acids. These bacteria also produce small amounts of vitamins, especially vitamin K, that can be absorbed into the blood. Although this source of vitamins generally provides only a small part of the normal daily requirement, it may make a significant contribution when dietary vitamin intake is low. An individual who depends on absorption of vitamins formed by bacteria in the large intestine may become vitamin deficient if treated with antibiotics that inhibit other species of bacteria as well as the disease-causing bacteria.

Other bacterial products include gas (**flatus**), which is a mixture of nitrogen and carbon dioxide,



**FIGURE 17–33**

The large intestine begins with the cecum. ✂

with small amounts of the inflammable gases hydrogen, methane, and hydrogen sulfide. Bacterial fermentation of undigested polysaccharides produces these gases in the colon (except for nitrogen, which is derived from swallowed air), at the rate of about 400 to 700 ml/day. Certain foods (beans, for example) contain large amounts of carbohydrates that cannot be digested by intestinal enzymes but are readily metabolized by bacteria in the large intestine, producing large amounts of gas.

**Motility and Defecation** Contractions of the circular smooth muscle in the large intestine produce a segmentation motion with a rhythm considerably slower (one every 30 min) than that in the small intestine. Because of the slow propulsion of the large intestine contents, material entering the large intestine from the small intestine remains for about 18 to 24 h. This provides time for bacteria to grow and multiply. Three to four times a day, generally following a meal, a wave of intense contraction, known as a **mass movement**, spreads rapidly over the transverse segment of the large intestine toward the rectum. This usually coincides with the gastroileal reflex. Unlike a peristaltic wave, in which the smooth muscle at each point relaxes after the wave of contraction has passed, the smooth muscle of the large intestine remains contracted for some time after a mass movement.

The **anus**, the exit from the rectum, is normally closed by the **internal anal sphincter**, which is composed of smooth muscle, and the **external anal sphincter**, which is composed of skeletal muscle under voluntary control. The sudden distension of the walls of the rectum produced by the mass movement of fecal material into it initiates the neurally mediated **defecation reflex**.

The conscious urge to defecate, mediated by mechanoreceptors, accompanies distension of the rectum. The reflex response consists of a contraction of the rectum, relaxation of the internal anal sphincter, but *contraction* of the external anal sphincter (initially), and increased peristaltic activity in the sigmoid colon. Eventually, a pressure is reached in the rectum that triggers reflex *relaxation* of the external anal sphincter, allowing the feces to be expelled.

Brain centers can, however, via descending pathways to somatic nerves to the external anal sphincter, override the reflex signals that eventually would relax the sphincter, thereby keeping the external sphincter closed and allowing a person to delay defecation. In this case, the prolonged distension of the rectum initiates a reverse peristalsis, driving the rectal contents back into the sigmoid colon. The urge to defecate then subsides until the next mass movement again propels more feces into the rectum, increasing its volume and

again initiating the defecation reflex. Voluntary control of the external anal sphincter is learned during childhood. Spinal-cord damage can lead to a loss of voluntary control over defecation.

Defecation is normally assisted by a deep inspiration, followed by closure of the glottis and contraction of the abdominal and thoracic muscles, producing an increase in abdominal pressure that is transmitted to the contents of the large intestine and rectum. This maneuver (termed the Valsalva maneuver) also causes a rise in intrathoracic pressure, which leads to a transient rise in blood pressure followed by a fall in pressure as the venous return to the heart is decreased. The cardiovascular changes resulting from excessive strain during defecation may precipitate a stroke or heart attack, especially in constipated elderly individuals with cardiovascular disease.

## Pathophysiology of the Gastrointestinal Tract

Since the end result of gastrointestinal function is the absorption of nutrients, salts, and water, most malfunctions of this organ system affect either the nutritional state of the body or its salt and water content. The following provide a few examples of disordered gastrointestinal function.

### Ulcers

Considering the high concentration of acid and pepsin secreted by the stomach, it is natural to wonder why the stomach does not digest itself. Several of the factors that protect the walls of the stomach from being digested are: (1) The surface of the mucosa is lined with cells that secrete a slightly alkaline mucus, which forms a thin layer over the luminal surface. Both the protein content of mucus and its alkalinity neutralize hydrogen ions in the immediate area of the epithelium. Thus, mucus forms a chemical barrier between the highly acid contents of the lumen and the cell surface. (2) The tight junctions between the epithelial cells lining the stomach restrict the diffusion of hydrogen ions into the underlying tissues. (3) Damaged epithelial cells are replaced every few days by new cells arising by the division of cells within the gastric pits.

Yet these protective mechanisms can prove inadequate, and erosion (**ulcers**) of the gastric surface occur. Ulcers can occur not only in the stomach but also in the lower part of the esophagus and in the duodenum. Indeed, duodenal ulcers are about 10 times more frequent than gastric ulcers, affecting about 10 percent of the U.S. population. Damage to blood vessels in the tissues underlying the ulcer may cause bleeding into the gastrointestinal lumen. On occasion, the ulcer may



penetrate the entire wall, resulting in leakage of the luminal contents into the abdominal cavity.

Ulcer formation involves breaking the mucosal barrier and exposing the underlying tissue to the corrosive action of acid and pepsin, but it is not always clear what produces the initial damage to the barrier. Although acid is essential for ulcer formation, it is not necessarily the primary factor, and many patients with ulcers have normal or even subnormal rates of acid secretion.

Many factors, including genetic susceptibility, drugs, alcohol, bile salts, and an excessive secretion of acid and pepsin, may contribute to ulcer formation. The major factor, however, is the presence of a bacterium, *Helicobacter pylori*, that is present in the stomachs of a majority of patients with ulcers or *gastritis* (inflammation of the stomach walls). Suppression of these bacteria with antibiotics usually leads to healing of the damaged mucosa.

Once an ulcer has formed, inhibition of acid secretion can remove the constant irritation and allow the ulcer to heal. Two classes of drugs are potent inhibitors of acid secretion. One class of inhibitors acts by blocking a specific class of histamine receptors found on parietal cells, which stimulate acid secretion. The second class of drugs directly inhibits the H,K-ATPase pump in parietal cells. Although both classes of drugs are effective in healing ulcers, if the *Helicobacter pylori* bacteria are not removed, the ulcers tend to recur.

Despite popular notions that ulcers are due to emotional stress and despite the existence of a potential pathway (the parasympathetic nerves) for mediating stress-induced increases in acid secretion, the role of stress in producing ulcers remains unclear. Once the ulcer has been formed, however, emotional stress can aggravate it by increasing acid secretion.

### Vomiting

Vomiting is the forceful expulsion of the contents of the stomach and upper intestinal tract through the mouth. Like swallowing, vomiting is a complex reflex coordinated by a region in the brainstem medulla oblongata, in this case known as the **vomiting center**. Neural input to this center from receptors in many different regions of the body can initiate the vomiting reflex. For example, excessive distension of the stomach or small intestine, various substances acting upon chemoreceptors in the intestinal wall or in the brain, increased pressure within the skull, rotating movements of the head (motion sickness), intense pain, and tactile stimuli applied to the back of the throat can all initiate vomiting.

What is the adaptive value of this reflex? Obviously, the removal of ingested toxic substances before they can be absorbed is of benefit. Moreover, the

nausea that usually accompanies vomiting may have the adaptive value of conditioning the individual to avoid the future ingestion of foods containing such toxic substances. Why other types of stimuli, such as those producing motion sickness, have become linked to the vomiting center is not clear.

Vomiting is usually preceded by increased salivation, sweating, increased heart rate, pallor, and feelings of nausea. The events leading to vomiting begin with a deep inspiration, closure of the glottis, and elevation of the soft palate. The abdominal muscles then contract, raising the abdominal pressure, which is transmitted to the stomach's contents. The lower esophageal sphincter relaxes, and the high abdominal pressure forces the contents of the stomach into the esophagus. This initial sequence of events can occur repeatedly without expulsion via the mouth and is known as *retching*. Vomiting occurs when the abdominal contractions become so strong that the increased intrathoracic pressure forces the contents of the esophagus through the upper esophageal sphincter.

Vomiting is also accompanied by strong contractions in the upper portion of the small intestine, contractions that tend to force some of the intestinal contents back into the stomach from which they can be expelled. Thus, some bile may be present in the vomitus.

Excessive vomiting can lead to large losses from the stomach of the water and salts that normally would be absorbed in the small intestine. This can result in severe dehydration, upset the body's salt balance, and produce circulatory problems due to a decrease in plasma volume. The loss of acid from vomiting results in a metabolic alkalosis (Chapter 16).

### Gallstones

As described earlier, bile contains not only bile salts but also cholesterol and phospholipids, which are water-insoluble and are maintained in soluble form in the bile as micelles. When the concentration of cholesterol in the bile becomes high in relation to the concentrations of phospholipid and bile salts, cholesterol crystallizes out of solution, forming *gallstones*. This can occur if the liver secretes excessive amounts of cholesterol or if the cholesterol becomes overly concentrated in the gallbladder as a result of salt and water absorption. Although cholesterol gallstones are the most frequently encountered gallstones in the Western world, the precipitation of bile pigments can also occasionally be responsible for gallstone formation.

Why some individuals develop gallstones and others do not is still unclear. Women, for example, have about twice the incidence of gallstone formation as men, and Native Americans have a very high incidence compared with other ethnic groups in the United States.



If a gallstone is small, it may pass through the common bile duct into the intestine with no complications. A larger stone may become lodged in the opening of the gallbladder, causing painful contractile spasms of the smooth muscle. A more serious complication arises when a gallstone lodges in the common bile duct, thereby preventing bile from entering the intestine. The absence of bile in the intestine decreases the rate of fat digestion and absorption, so that approximately half of ingested fat is not digested and passes on to the large intestine and eventually appears in the feces. Furthermore, bacteria in the large intestine convert some of this fat into fatty acid derivatives that alter salt and water movements, leading to a net flow of fluid into the large intestine. The result is diarrhea and fluid loss.

Since the duct from the pancreas joins the common bile duct just before it enters the duodenum, a gallstone that becomes lodged at this point prevents both bile and pancreatic secretions from entering the intestine. This results in failure both to neutralize acid and to digest adequately most organic nutrients, not just fat. The end result is severe nutritional deficiencies.

The buildup of pressure in a blocked common bile duct inhibits further secretion of bile. As a result, bilirubin, which is normally secreted into the bile from the blood, accumulates in the blood and diffuses into tissues, where it produces the yellowish coloration of the skin and eyes known as *jaundice*.

It should be emphasized, however, that bile duct obstruction is not the only cause of jaundice. Bilirubin accumulation in the blood can occur if hepatocytes are damaged by liver disease and therefore fail to secrete bilirubin into the bile. It can also occur if the level of bilirubin in the blood exceeds the capacity of the normal liver to secrete it, as in diseases that result in an increased breakdown of red blood cells—*hemolytic jaundice*. At birth, the liver's capacity to secrete bilirubin is not fully developed. During the first few days of life this may result in jaundice, which normally clears spontaneously. Excessive accumulation of bilirubin during the neonatal period, as occurs, for example, with hemolytic disease of the newborn (Chapter 20), carries a risk of bilirubin-induced neurological damage at a time when a critical phase in the development of the nervous system is occurring.

Although surgery may be necessary to remove an inflamed gallbladder or stones from an obstructed duct, newer techniques use drugs to dissolve gallstones or noninvasive ultrasound to shatter gallstones.

### Lactose Intolerance

Lactose is the major carbohydrate in milk. It cannot be absorbed directly but must first be digested into its components—glucose and galactose—which are

readily absorbed by active transport. Lactose is digested by the enzyme **lactase**, which is embedded in the luminal plasma membranes of intestinal epithelial cells. Lactase is present at birth, but in approximately 25 percent of white Americans and in most Asians, its concentration begins to decline when the child is between 18 and 36 months old. This decline in lactase is genetically determined. In these individuals, as the lactase declines ingested lactose cannot be completely digested—a condition known as *lactose intolerance*—and some lactose remains in the small intestine.

Since the absorption of water requires prior absorption of solute to provide an osmotic gradient, the unabsorbed lactose in persons with lactose intolerance prevents some of the water from being absorbed. This lactose-containing fluid is passed on to the large intestine, where bacteria digest the lactose. They then metabolize the released monosaccharides, producing large quantities of gas (which distends the colon, producing pain) and short-chain fatty acids, which cause fluid movement into the lumen of the large intestine, producing diarrhea. The response to milk ingestion by adults whose lactase levels have diminished varies from mild discomfort to severely dehydrating diarrhea, according to the volume of milk and milk products ingested and the amount of lactase present in the intestine. These symptoms can be avoided if the person either drinks milk in which the lactose has been predigested or takes pills containing lactase along with the milk.

### Constipation and Diarrhea

Many people have a mistaken belief that, unless they have a bowel movement every day, the absorption of “toxic” substances from fecal material in the large intestine will somehow poison them. Attempts to identify such toxic agents in the blood following prolonged periods of fecal retention have been unsuccessful, and there appears to be no physiological necessity for having bowel movements at frequent intervals. Whatever maintains a person in a comfortable state is physiologically adequate, whether this means a bowel movement after every meal, once a day, or only once a week.

On the other hand, there often are symptoms—headache, loss of appetite, nausea, and abdominal distension—that may arise when defecation has not occurred for several days or even weeks, depending on the individual. These symptoms of *constipation* are caused not by toxins but by distension of the rectum. The longer that fecal material remains in the large intestine, the more water is absorbed and the harder and drier the feces become, making defecation more difficult and sometimes painful. Thus, constipation tends to promote constipation.

Decreased motility of the large intestine is the primary factor causing constipation. This often occurs in the elderly, or it may result from damage to the colon's enteric nervous system or from emotional stress.

One of the factors increasing motility in the large intestine, and thus opposing the development of constipation, is distension. As noted earlier, dietary fiber (cellulose and other complex polysaccharides) is not digested by the enzymes in the small intestine and is passed on to the large intestine, where its bulk produces distension and thereby increases motility. Bran, most fruits, and vegetables are examples of foods that have a relatively high fiber content.

**Laxatives**, agents that increase the frequency or ease of defecation, act through a variety of mechanisms. Thus, fiber provides a natural laxative. Some laxatives, such as mineral oil, simply lubricate the feces, making defecation easier and less painful. Others contain magnesium and aluminum salts, which are poorly absorbed and therefore lead to water retention in the intestinal tract. Still others, such as castor oil, stimulate the motility of the colon and inhibit ion transport across the wall, thus affecting water absorption.

Excessive use of laxatives in an attempt to maintain a preconceived notion of regularity leads to a decreased responsiveness of the large intestine to normal defecation-promoting signals. In such cases, a long period without defecation may occur following cessation of laxative intake, appearing to confirm the necessity of taking laxatives to promote regularity.

**Diarrhea** is characterized by large, frequent, watery stools. Diarrhea can result from decreased fluid absorption, increased fluid secretion, or both. The increased motility that accompanies diarrhea probably does not *cause* most cases of diarrhea (by decreasing the time available for fluid absorption) but rather is a result of the distension produced by increased luminal fluid.

A number of bacterial, protozoan, and viral diseases of the intestinal tract cause secretory diarrhea. **Cholera**, which is endemic in many parts of the world, is caused by a bacterium that releases a toxin that stimulates the production of cyclic AMP in the secretory cells at the base of the intestinal villi. This leads to an increased frequency of opening of the chloride channels in the luminal membrane and hence increased secretion of chloride ions. There is an accompanying osmotic flow of water into the intestinal lumen, resulting in massive diarrhea that can be life-threatening due to dehydration and decreased blood volume that leads to circulatory shock. The salt and water lost by this severe form of diarrhea can be balanced by ingesting a simple solution containing salt and glucose. The active absorption of these solutes is accompanied by absorption of water, which replaces the fluid lost by diarrhea.

**Traveler's diarrhea**, produced by several species of bacteria, produces a secretory diarrhea by the same mechanism as the cholera bacterium, but is less severe.

In addition to decreased blood volume due to the salt and water loss, other consequences of severe diarrhea are potassium depletion and metabolic acidosis (Chapter 16) resulting from the excessive fecal loss of potassium and bicarbonate ions, respectively.

#### S U M M A R Y

- I. The gastrointestinal system transfers digested organic nutrients, minerals, and water from the external environment to the internal environment. The four processes used to accomplish this function are (a) digestion, (b) secretion, (c) absorption, and (d) motility.
  - a. The system is designed to maximize the absorption of most nutrients, not to regulate the amount absorbed.
  - b. The system does not play a major role in the removal of waste products from the internal environment.

#### Overview: Functions of the Gastrointestinal Organs

- I. The names and functions of the gastrointestinal organs are summarized in Figure 17-3.
- II. Each day the gastrointestinal tract secretes about 6 times more fluid into the lumen than is ingested. Only 1 percent of this fluid is excreted in the feces.

#### Structure of the Gastrointestinal Tract Wall

- I. The structure of the wall of the gastrointestinal tract is summarized in Figure 17-6.
  - a. The area available for absorption in the small intestine is greatly increased by the folding of the intestinal wall and by the presence of villi and microvilli on the surface of the epithelial cells.
  - b. The epithelial cells lining the intestinal tract are continuously replaced by new cells arising from cell division at the base of the villi.
  - c. The venous blood from the small intestine, containing absorbed nutrients other than fat, passes to the liver via the hepatic portal vein before returning to the heart. Fat is absorbed into the lymphatic vessels (lacteals) in each villus.

#### Digestion and Absorption

- I. Starch is digested by amylases secreted by the salivary glands and pancreas, and the resulting products, as well as ingested disaccharides, are digested to monosaccharides by enzymes in the luminal membranes of epithelial cells in the small intestine.
  - a. Most monosaccharides are then absorbed by secondary active transport.

- b. Some polysaccharides, such as cellulose, cannot be digested and pass to the large intestine, where they are metabolized by bacteria.
- II. Proteins are broken down into small peptides and amino acids, which are absorbed by secondary active transport in the small intestine.
  - a. The breakdown of proteins to peptides is catalyzed by pepsin in the stomach and by the pancreatic enzymes trypsin and chymotrypsin in the small intestine.
  - b. Peptides are broken down into amino acids by pancreatic carboxypeptidase and intestinal aminopeptidase.
  - c. Small peptides consisting of two to three amino acids can be actively absorbed into epithelial cells and then broken down to amino acids, which are released into the blood.
- III. The digestion and absorption of fat by the small intestine requires mechanisms that solubilize the fat and its digestion products.
  - a. Large fat globules leaving the stomach are emulsified in the small intestine by bile salts and phospholipids secreted by the liver.
  - b. Lipase from the pancreas digests fat at the surface of the emulsion droplets, forming fatty acids and monoglycerides.
  - c. These water-insoluble products of lipase action, when combined with bile salts, form micelles, which are in equilibrium with the free molecules.
  - d. Free fatty acids and monoglycerides diffuse across the luminal membranes of epithelial cells, within which they are enzymatically recombined to form triacylglycerol, which is released as chylomicrons from the blood side of the cell by exocytosis.
  - e. The released chylomicrons enter lacteals in the intestinal villi and pass, by way of the lymphatic system, to the venous blood returning to the heart.
- IV. Fat-soluble vitamins are absorbed by the same pathway used for fat absorption. Most water-soluble vitamins are absorbed in the small intestine by diffusion or mediated transport. Vitamin B<sub>12</sub> is absorbed in the ileum by endocytosis after combining with intrinsic factor secreted into the lumen by parietal cells in the stomach.
- V. Water is absorbed from the small intestine by osmosis following the active absorption of solutes, primarily sodium chloride.
- b. Endocrine cells scattered throughout the epithelium of the stomach secrete gastrin, and cells in the small intestine secrete secretin, CCK, and GIP. The properties of these hormones are summarized in Table 17–3.
- c. The three phases of gastrointestinal regulation—cephalic, gastric, and intestinal—are named for the location of the stimulus that initiates the response.
  - II. Chewing breaks up food into particles suitable for swallowing, but it is not essential for the eventual digestion and absorption of food.
  - III. Salivary secretion is stimulated by food in the mouth acting reflexly via chemoreceptors and pressure receptors. Both sympathetic and parasympathetic stimulation increase salivary secretion.
  - IV. Food moved into the pharynx by the tongue initiates swallowing, which is coordinated by the swallowing center in the brainstem medulla oblongata.
    - a. Food is prevented from entering the trachea by inhibition of respiration and by closure of the glottis.
    - b. The upper esophageal sphincter relaxes as food is moved into the esophagus, and then the sphincter closes.
    - c. Food is moved through the esophagus toward the stomach by peristaltic waves. The lower esophageal sphincter remains open throughout swallowing.
    - d. If food does not reach the stomach with the first peristaltic wave, distension of the esophagus initiates secondary peristalsis.
  - V. The factors controlling acid secretion by parietal cells in the stomach are summarized in Table 17–4.
  - VI. Pepsinogen, secreted by the gastric chief cells in response to most of the same reflexes that control acid secretion, is converted to the active proteolytic enzyme pepsin in the stomach’s lumen by acid and by activated pepsin.
  - VII. Peristaltic waves sweeping over the stomach become stronger in the antrum, where most mixing occurs. With each wave, only a small portion of the stomach’s contents are expelled into the small intestine through the pyloric sphincter.
    - a. Cycles of membrane depolarization, the basic electrical rhythm generated by gastric smooth muscle, determine gastric peristaltic wave frequency. Contraction strength can be altered by neural and hormonal changes in membrane potential, which is imposed on the basic electrical rhythm.
    - b. Distension of the stomach increases the force of contractions and the rate of emptying. Distension of the small intestine, and fat, acid, or hypertonic solutions in the intestinal lumen inhibit gastric contractions.
- VIII. The exocrine portion of the pancreas secretes digestive enzymes and bicarbonate ions, all of which reach the duodenum through the pancreatic duct.

### Regulation of Gastrointestinal Processes

- I. Most gastrointestinal reflexes are initiated by luminal stimuli: (a) distension, (b) osmolarity, (c) acidity, and (d) digestion products.
  - a. Neural reflexes are mediated by short reflexes in the enteric nervous system and by long reflexes involving afferent and efferent neurons to and from the CNS.

- a. The bicarbonate ions neutralize acid entering the small intestine from the stomach.
  - b. Most of the proteolytic enzymes, including trypsin, are secreted by the pancreas in inactive forms. Trypsin is activated by enterokinase located on the membranes of the small-intestine cells and in turn activates other inactive pancreatic enzymes.
  - c. The hormone secretin, released from the small intestine in response to increased luminal acidity, stimulates pancreatic bicarbonate secretion. CCK is released from the small intestine in response to the products of fat and protein digestion, and stimulates pancreatic enzyme secretion.
  - d. Parasympathetic stimulation increases pancreatic secretion.
- IX. The liver secretes bile, the major ingredients of which are bile salts, cholesterol, lecithin, bicarbonate ions, bile pigments, and trace metals.
- a. Bile salts undergo continuous enterohepatic recirculation during a meal. The liver synthesizes new bile salts to replace those lost in the feces.
  - b. The greater the bile salt concentration in the hepatic portal blood, the greater the rate of bile secretion.
  - c. Bilirubin, the major bile pigment, is a breakdown product of hemoglobin and is absorbed from the blood by the liver and secreted into the bile.
  - d. Secretin stimulates bicarbonate secretion by the cells lining the bile ducts in the liver.
  - e. Bile is concentrated in the gallbladder by the absorption of NaCl and water.
  - f. Following a meal, the release of CCK from the small intestine causes the gallbladder to contract and the sphincter of Oddi to relax, thereby injecting concentrated bile into the intestine.
- X. In the small intestine, the digestion of polysaccharides and proteins increases the osmolarity of the luminal contents, producing water flow into the lumen.
- XI. Sodium, chloride, bicarbonate, and water are secreted by the small intestine. However, most of these secreted substances, as well as those entering the small intestine from other sources, are absorbed back into the blood.
- XII. Intestinal motility is coordinated by the enteric nervous system and modified by long and short reflexes and hormones.
- a. During and shortly after a meal, the intestinal contents are mixed by segmenting movements of the intestinal wall.
  - b. After most of the food has been digested and absorbed, segmentation is replaced by the migrating motility complex, which moves the undigested material into the large intestine by a migrating segment of peristaltic waves.
- XIII. The primary function of the large intestine is to store and concentrate fecal matter before defecation.
- a. Water is absorbed from the large intestine secondary to the active absorption of sodium, leading to the concentration of fecal matter.
  - b. Flatus is produced by bacterial fermentation of undigested polysaccharides.
  - c. Three to four times a day, mass movements in the colon move its contents into the rectum.
  - d. Distension of the rectum initiates defecation, which is assisted by a forced expiration against a closed glottis.
  - e. Defecation can be voluntarily controlled through somatic nerves to the skeletal muscles of the external anal sphincter.

### Pathophysiology of the Gastrointestinal Tract

- I. The factors that normally prevent breakdown of the mucosal barrier and formation of ulcers are (1) secretion of an alkaline mucus, (2) tight junctions between epithelial cells, and (3) rapid replacement of epithelial cells.
  - a. The bacterium *Helicobacter pylori* is a major cause of damage to the mucosal barrier leading to ulcers.
  - b. Drugs that block histamine receptors or inhibit the H,K-ATPase pump inhibit acid secretion and promote ulcer healing.
- II. Vomiting is coordinated by the vomiting center in the brainstem medulla oblongata. Contractions of abdominal muscles force the contents of the stomach into the esophagus (retching), and if the contractions are strong enough, they force the contents of the esophagus through the upper esophageal sphincter into the mouth (vomiting).
- III. Precipitation of cholesterol or, less often, bile pigments in the gallbladder forms gallstones, which can block the exit of the gallbladder or common bile duct. In the latter case, the failure of bile salts to reach the intestine causes decreased digestion and absorption of fat, and the accumulation of bile pigments in the blood and tissues causes jaundice.
- IV. Lactase, which is present at birth, undergoes a genetically determined decrease during childhood in many individuals. In the absence of lactase, lactose cannot be digested, and its presence in the small intestine can result in diarrhea and increased flatus production when milk is ingested.
- V. Constipation is primarily the result of decreased colonic motility. The symptoms of constipation are produced by overdistension of the rectum, not by the absorption of toxic bacterial products.
- VI. Diarrhea can be caused by decreased fluid absorption, increased fluid secretion, or both.

KEY TERMS

gastrointestinal (GI) system	long reflex
gastrointestinal tract	secretin
digestion	cholecystokinin (CCK)
secretion	gastrin
absorption	glucose-dependent
motility	insulinotropic peptide (GIP)
feces	potentiation
mouth	cephalic phase
saliva	gastric phase
salivary gland	intestinal phase
amylase	swallowing center
pharynx	glottis
esophagus	epiglottis
stomach	upper esophageal sphincter
hydrochloric acid	lower esophageal sphincter
pepsin	peristaltic waves
chyme	secondary peristalsis
small intestine	body (of stomach)
duodenum	fundus
jejunum	pepsinogen
ileum	antrum
pancreas	parietal cell
liver	chief cell
hepatic	enterochromaffin-like (ECL) cell
bile	somatostatin
bile salt	enterogastrone
gallbladder	zymogen
common bile duct	receptive relaxation
large intestine	pyloric sphincter
rectum	basic electrical rhythm
defecation	enterokinase
mucosa	trypsinogen
submucous plexus	bile canaliculi
muscularis externa	enterohepatic circulation
circular muscle	bile pigment
longitudinal muscle	bilirubin
myenteric plexus	hepatocyte
serosa	sphincter of Oddi
villi	segmentation
microvilli	migrating motility complex
lacteal	motilin
hepatic portal vein	gastroileal reflex
fiber	intestino-intestinal reflex
trypsin	cecum
chymotrypsin	appendix
carboxypeptidase	colon
aminopeptidase	ileocecal sphincter
lipase	flatus
emulsification	mass movement
micelle	anus
colipase	internal anal sphincter
chylomicron	external anal sphincter
intrinsic factor	defecation reflex
enteric nervous system	vomiting center
short reflex	lactase

REVIEW QUESTIONS

- List the four processes that accomplish the functions of the gastrointestinal system.
- List the primary functions performed by each of the organs in the gastrointestinal system.
- Approximately how much fluid is secreted into the gastrointestinal tract each day compared with the amount of food and drink ingested? How much of this appears in the feces?
- What structures are responsible for the large surface area of the small intestine?
- Where does the venous blood go after leaving the small intestine?
- Identify the enzymes involved in carbohydrate digestion and the mechanism of carbohydrate absorption in the small intestine.
- List three ways in which proteins or their digestion products can be absorbed from the small intestine.
- Describe the process of fat emulsification.
- What is the role of micelles in fat absorption?
- Describe the movement of fat digestion products from the intestinal lumen to a lacteal.
- How does the absorption of fat-soluble vitamins differ from that of water-soluble vitamins?
- Specify two conditions that may lead to failure to absorb vitamin B<sub>12</sub>.
- How are salts and water absorbed in the small intestine?
- Describe the role of ferritin in the absorption of iron.
- List the four types of stimuli that initiate most gastrointestinal reflexes.
- Describe the location of the enteric nervous system and its role in both short and long reflexes.
- Name the four established gastrointestinal hormones and state their major functions.
- Describe the neural reflexes leading to increased salivary secretion.
- Describe the sequence of events that occur during swallowing.
- List the cephalic, gastric, and intestinal phase stimuli that stimulate or inhibit acid secretion by the stomach.
- Describe the function of gastrin and the factors controlling its secretion.
- By what mechanism is pepsinogen converted to pepsin in the stomach?
- Describe the factors that control gastric emptying.
- Describe the mechanisms controlling pancreatic secretion of bicarbonate and enzymes.
- How are pancreatic proteolytic enzymes activated in the small intestine?
- List the major constituents of bile.
- Describe the recycling of bile salts by the enterohepatic circulation.
- What determines the rate of bile secretion by the liver?
- Describe the effects of secretin and CCK on the bile ducts and gallbladder.



30. What causes water to move from the blood to the lumen of the duodenum following gastric emptying?
31. Describe the type of intestinal motility found during and shortly after a meal and the type found several hours after a meal.
32. Describe the production of flatus by the large intestine.
33. Describe the factors that initiate and control defecation.
34. Why is the stomach's wall normally not digested by the acid and digestive enzymes in the lumen?
35. Describe the process of vomiting.
36. What are the consequences of blocking the common bile duct with a gallstone?
37. What are the consequences of the failure to digest lactose in the small intestine?
38. Contrast the factors that cause constipation with those that produce diarrhea.

#### CLINICAL TERMS

pernicious anemia	gallstones
hemochromatosis	jaundice
heartburn	hemolytic jaundice
gastro-esophageal reflux	lactose intolerance
dumping syndrome	constipation
ulcers	laxatives
<i>Helicobacter pylori</i>	diarrhea
gastritis	cholera
retching	traveler's diarrhea

#### THOUGHT QUESTIONS

(Answers are given in Appendix A.)

1. If the salivary glands were unable to secrete amylase, what effect would this have on starch digestion?
2. Whole milk or a fatty snack consumed before the ingestion of alcohol decreases the rate of intoxication. By what mechanism may fat be acting to produce this effect?
3. A patient brought to a hospital after a period of prolonged vomiting has an elevated heart rate, decreased blood pressure, and below-normal blood acidity. Explain these symptoms in terms of the consequences of excessive vomiting.
4. Can fat be digested and absorbed in the absence of bile salts? Explain.
5. How might damage to the lower portion of the spinal cord affect defecation?
6. One of the older but no longer used procedures in the treatment of ulcers is vagotomy, surgical cutting of the vagus (parasympathetic) nerves to the stomach. By what mechanism might this procedure help ulcers to heal and decrease the incidence of new ulcers?