Case Investigation

Alan, a 23-year-old student, went to the health center complaining of severe but transient stomach pain whenever he drank wine, and pain below his right scapula whenever he ate particular foods, such as peanut butter or bacon, but not when he ate skinned chicken or fish. The physician noticed that the sclera of Alan's eyes were markedly yellow, and ordered a stool sample and a variety of blood tests to be performed.

Some of the new terms and concepts you will encounter include:

- Free and conjugated bilirubin; jaundice
- Urea, ammonia, and pancreatic amylase
- Appendicitis; gallstones; and cholecystokinin

18.1 INTRODUCTION TO THE DIGESTIVE SYSTEM

Within the lumen of the gastrointestinal tract, large food molecules are hydrolyzed into their monomers (subunits). These monomers pass through the inner layer, or mucosa, of the small intestine to enter the blood or lymph in a process called absorption. Digestion and absorption are aided by specializations of the gastrointestinal tract.

LEARNING OUTCOMES

After studying this section, you should be able to:

- ✔ List the functions of the digestive system
- ✔ Describe the microscopic structure of the gastrointestinal tract

Unlike plants, which can form organic molecules using inorganic compounds such as carbon dioxide, water, and ammonia, humans and other animals must obtain their basic organic molecules from food. Some of the ingested food molecules are needed for their energy (caloric) value—obtained by the reactions of cell respiration and used in the production of ATP—and the balance is used to make additional tissue.

Most of the organic molecules that are ingested are similar to the molecules that form human tissues. These are generally large molecules (*polymers*), which are composed of subunits (*monomers*). Within the gastrointestinal tract, the **digestion** of these large molecules into their monomers occurs by means of *hydrolysis reactions* (reviewed in fig. 18.1). The monomers thus formed are transported across the wall of the small intestine into the blood and lymph in the process of **absorption.** Digestion and absorption are the primary functions of the digestive system.

Because the composition of food is similar to the composition of body tissues, enzymes that digest food are also capable of digesting a person's own tissues. This does not normally occur, however, because a variety of protective devices inactivate digestive enzymes in the body and keep them away from the cytoplasm of the cells. The fully active digestive enzymes are normally confined to the lumen (cavity) of the gastrointestinal tract.

The lumen of the gastrointestinal tract is open at both ends (mouth and anus) and is thus continuous with the environment. In this sense, the harsh conditions required for digestion occur *outside* the body. Indigestible materials, such as cellulose from plant walls, pass from one end to the other without crossing the epithelial lining of the digestive tract; because they are not absorbed, they do not enter the body.

In *Planaria* (a type of flatworm), the gastrointestinal tract has only one opening—the mouth is also the anus. Each cell that lines the gastrointestinal tract is thus exposed to food, absorbable digestion products, and waste products. The two open ends of the digestive tract of higher organisms, by contrast, permit one-way transport, which is ensured by wavelike muscle contractions and by the action of sphincter muscles. This one-way transport allows different regions of the gastrointestinal tract to be specialized for different functions, as a "dis-assembly line." These functions of the digestive system include:

1. **Motility.** This refers to the movement of food through the digestive tract through the processes of
   a. *Ingestion:* Taking food into the mouth.
   b. *Mastication:* Chewing the food and mixing it with saliva.
   c. *Deglutition:* Swallowing food.
   d. *Peristalsis* and *segmentation:* Rhythmic, wavelike contractions (peristalsis), and mixing contractions in different segments (segmentation), move food through the gastrointestinal tract.
2. **Secretion.** This includes both exocrine and endocrine secretions.
   a. *Exocrine secretions:* Water, hydrochloric acid, bicarbonate, and many digestive enzymes are secreted into the lumen of the gastrointestinal tract. The stomach alone, for example, secretes 2 to 3 liters of gastric juice a day.
   b. *Endocrine secretions:* The stomach and small intestine secrete a number of hormones that help to regulate the digestive system.
3. **Digestion.** This refers to the breakdown of food molecules into their smaller subunits, which can be absorbed.
4. **Absorption.** This refers to the passage of digested end products into the blood or lymph.
5. **Storage and elimination.** This refers to the temporary storage and subsequent elimination of indigestible food molecules.
6. **Immune barrier.** The simple columnar epithelium that lines the intestine, with its tight junctions between

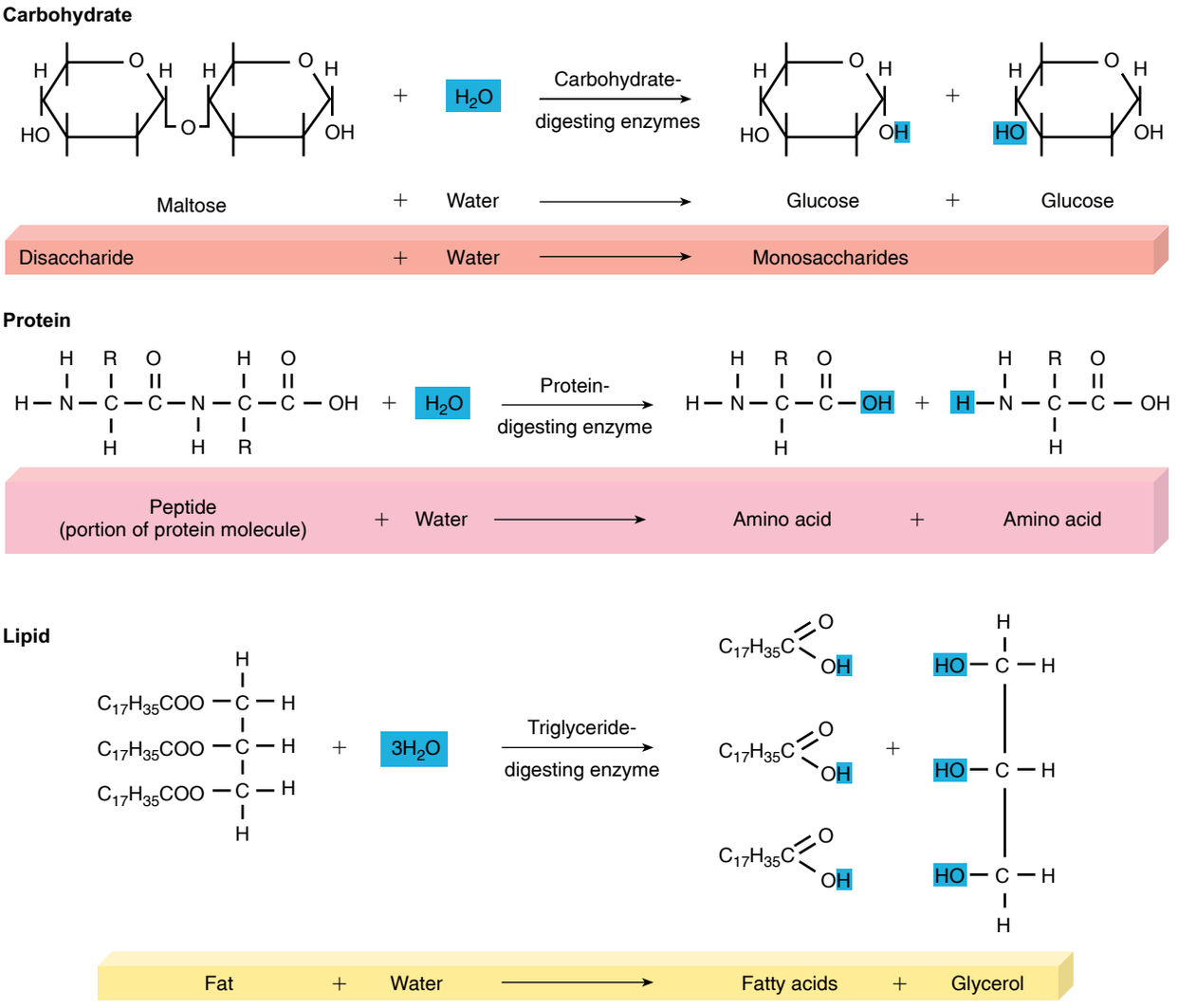

Figure 18.1 **The digestion of food molecules through hydrolysis reactions.** These reactions ultimately release the subunit molecules of each food category.

cells, provides a physical barrier to the penetration of pathological organisms and their toxins. Also, cells of the immune system reside in the connective tissue located just under the epithelium (see fig. 18.3) to promote immune responses.

Anatomically and functionally, the digestive system can be divided into the tubular **gastrointestinal (GI) tract,** or *alimentary canal,* and **accessory digestive organs.** The GI tract is approximately 9 m (30 ft) long and extends from the mouth to the anus. It traverses the thoracic cavity and enters the abdominal cavity at the level of the diaphragm. The anus is located at the inferior portion of the pelvic cavity. The organs of the GI tract include the *oral cavity, pharynx, esophagus, stomach, small intestine,* and *large intestine* (fig. 18.2). The accessory digestive organs include the *teeth, tongue, salivary glands, liver, gallbladder,* and *pancreas.* The term *viscera* is frequently used to refer to the abdominal organs of digestion, but it also can be used in reference to any of the organs in the thoracic and abdominal cavities.

Layers of the Gastrointestinal Tract

The GI tract from the esophagus to the anal canal is composed of four layers, or *tunics.* Each tunic contains a dominant tissue type that performs specific functions in the digestive process. The four tunics of the GI tract, from the inside out, are the *mucosa, submucosa, muscularis,* and *serosa* (fig. 18.3*a*).

Mucosa

The **mucosa,** which lines the lumen of the GI tract, is the absorptive and major secretory layer. It consists of a simple columnar epithelium supported by the *lamina propria,* a thin layer of areolar connective tissue containing numerous lymph nodules, which are important in protecting against disease (fig. 18.3*b*). External to the lamina propria is a thin layer of smooth muscle called the *muscularis mucosae.* This is the muscle layer responsible for the numerous small folds in certain portions of the GI tract. These folds greatly

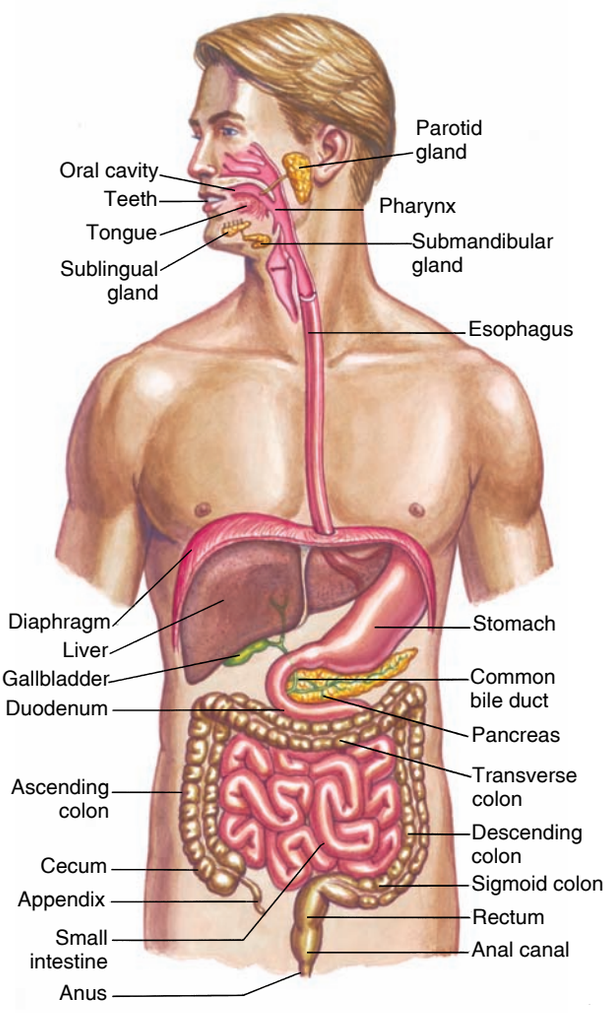

Figure 18.2 The organs of the digestive system. The digestive system includes the gastrointestinal tract and the accessory digestive organs.

increase the absorptive surface area. Specialized goblet cells in the mucosa secrete mucus throughout most of the GI tract.

Submucosa

The relatively thick **submucosa** is a highly vascular layer of connective tissue that serves the mucosa. Absorbed molecules that pass through the columnar epithelial cells of the mucosa enter into blood and lymphatic vessels of the submucosa. In addition to blood vessels, the submucosa contains glands and nerve plexuses. The **submucosal plexus** (*Meissner's plexus*) (fig. 18.3*b*) provides a nerve supply to the muscularis mucosae of the small and large intestine.

Muscularis

The **muscularis** (also called the *muscularis externa*) is responsible for segmental contractions and peristaltic movement through the GI tract. The muscularis has an inner circular and an outer longitudinal layer of smooth muscle. Contractions of these layers move the food through the tract and physically pulverize and mix the food with digestive enzymes. The **myenteric plexus** (*Auerbach's plexus*), located between the two muscle layers, provides the major nerve supply to the entire GI tract. It includes fibers and ganglia from both the sympathetic and parasympathetic divisions of the autonomic nervous system.

Serosa

The outer **serosa** completes the wall of the GI tract. It is a binding and protective layer consisting of areolar connective tissue covered with a layer of simple squamous epithelium.

Regulation of the Gastrointestinal Tract

The GI tract is innervated by the sympathetic and parasympathetic divisions of the autonomic nervous system. As discussed in chapter 9, parasympathetic nerves in general stimulate motility and secretions of the gastrointestinal tract. The vagus nerve is the source of parasympathetic activity in the esophagus, stomach, pancreas, gallbladder, small intestine, and upper portion of the large intestine. The lower portion of the large intestine receives parasympathetic innervation from spinal nerves in the sacral region. The submucosal plexus and myenteric plexus are the sites where parasympathetic preganglionic fibers synapse with postganglionic neurons that innervate the smooth muscle of the GI tract.

Postganglionic sympathetic fibers pass through the submucosal and myenteric plexuses and innervate the GI tract. The effects of the sympathetic nerves reduce peristalsis and secretory activity and stimulate the contraction of sphincter muscles along the GI tract; therefore, they are antagonistic to the effects of parasympathetic nerve stimulation.

Autonomic regulation, which is "extrinsic" to the gastrointestinal tract, is superimposed on "intrinsic" modes of regulation. The gastrointestinal tract contains **intrinsic sensory neurons** that have their cell bodies within the gut wall and are not part of the autonomic system. These help in the local regulation of the digestive tract by a complex neural network within the wall of the gut called the *enteric nervous system,* or *enteric brain* (discussed in section 18.6). Regulation by the enteric nervous system complements paracrine regulation by molecules acting locally within the tissues of the GI tract, as well as hormonal regulation by hormones secreted by the mucosa.

In summary, the digestive system is regulated extrinsically by the autonomic nervous system and endocrine system, and intrinsically by the enteric nervous system and various paracrine regulators. The details of this regulation will be described in subsequent sections.

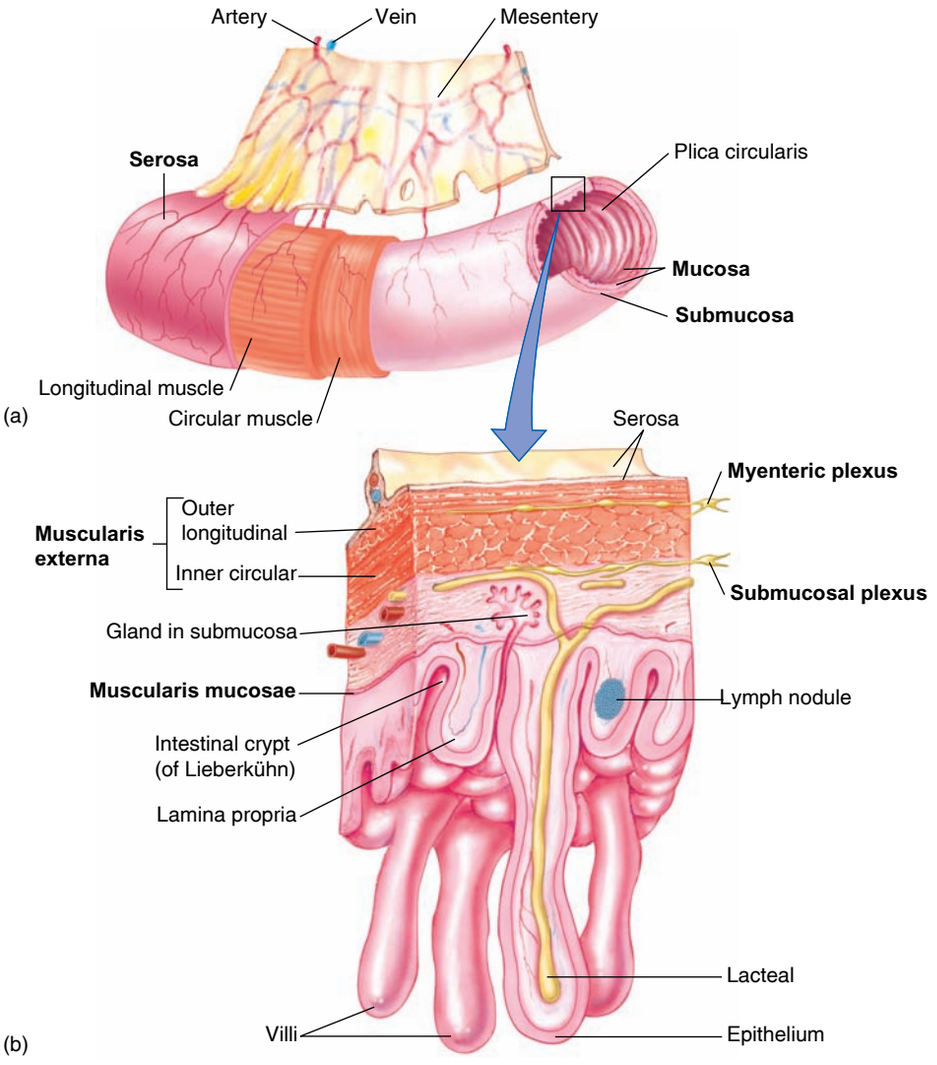

Figure 18.3 The layers of the digestive tract. (*a*) An illustration of the major tunics, or layers, of the small intestine. The inset shows how folds of mucosa form projections called villi in the small intestine. (*b*) An illustration of a cross section of the small intestine showing layers and glands.

✔ CHECKPOINT

1. Define the terms *digestion* and *absorption,* describe how molecules are digested, and indicate which molecules are absorbed.
2. Describe the structure and function of the mucosa, submucosa, and muscularis.
3. Describe the location and composition of the submucosal and myenteric plexuses and explain the actions of autonomic nerves on the gastrointestinal tract.

18.2 FROM MOUTH TO STOMACH

Peristaltic contractions of the esophagus deliver food to the stomach, which secretes very acidic gastric juice that is mixed with the food by gastric contractions. Proteins in the resulting mixture, called chyme, are partially digested by the enzyme pepsin.

LEARNING OUTCOMES

After studying this section, you should be able to:

- ✔ Describe the structure and functions of the esophagus and stomach
- ✔ Explain how gastric secretion is regulated

Mastication (chewing) of food mixes it with saliva, secreted by the salivary glands. In addition to mucus and various antimicrobial agents, saliva contains *salivary amylase,* an enzyme that can catalyze the partial digestion of starch. **Deglutition,** or swallowing, is divided into three phases: *oral, pharyngeal,* and *esophageal.* Swallowing is a complex activity that requires the coordinated contractions

of 25 pairs of muscles in the mouth, pharynx, larynx, and esophagus. The muscles of the mouth, pharynx, and upper esophagus are striated and innervated by somatic motor neurons, whereas the muscles of the middle and lower esophagus are smooth and innervated by autonomic neurons. The oral phase is under voluntary control, while the pharyngeal and esophageal phases are automatic and controlled by the **swallowing center** in the brain stem.

In the oral phase, the muscles of the mouth and tongue mix the food with saliva and create a *bolus* (a mass of a size to be swallowed) of food that the tongue muscles move toward the oropharynx. Receptors in the posterior portion of the oral cavity and oropharynx stimulate the pharyngeal phase of the swallowing reflex. The soft palate lifts to close off the nasopharynx from the oropharynx (so food does not go out the nose); the vocal cords close off the opening to the larynx, and the epiglottis covers the vocal cords; the larynx is moved away from the pathway of the bolus toward the esophagus (these activities help prevent choking); and the upper esophageal sphincter relaxes. These complex activities of the pharyngeal phase take less than 1 second. In the esophageal phase of swallowing, which lasts from 5 to 6 seconds, the bolus of food is moved by peristaltic contractions toward the stomach.

Once in the stomach, the ingested material is churned and mixed with hydrochloric acid and the protein-digesting enzyme pepsin. The mixture thus produced is pushed by muscular contractions of the stomach past the pyloric sphincter (*pylorus* = gatekeeper), which guards the junction of the stomach and the duodenum of the small intestine.

Esophagus

The **esophagus** is the portion of the GI tract that connects the pharynx to the stomach. It is a muscular tube approximately 25 cm (10 in.) long, located posterior to the trachea within the mediastinum of the thorax. Before terminating in the stomach, the esophagus passes through the diaphragm by means of an opening called the *esophageal hiatus.* The esophagus is lined with a nonkeratinized stratified squamous epithelium; its walls contain either skeletal or smooth muscle, depending on the location. The upper third of the esophagus contains skeletal muscle, the middle third contains a mixture of skeletal and smooth muscle, and the terminal portion contains only smooth muscle.

Swallowed food is pushed from the oral to the anal end of the esophagus (and, afterward, of the intestine) by a wavelike muscular contraction called **peristalsis** (fig. 18.4). Movement of the bolus along the digestive tract occurs because the circular smooth muscle contracts behind, and relaxes in front of, the bolus. This is followed by shortening of the tube by longitudinal muscle contraction. These contractions progress from the superior end of the esophagus to the *gastroesophageal junction* at a rate of 2 to 4 cm per second as they empty the contents of the esophagus into the cardiac region of the stomach.

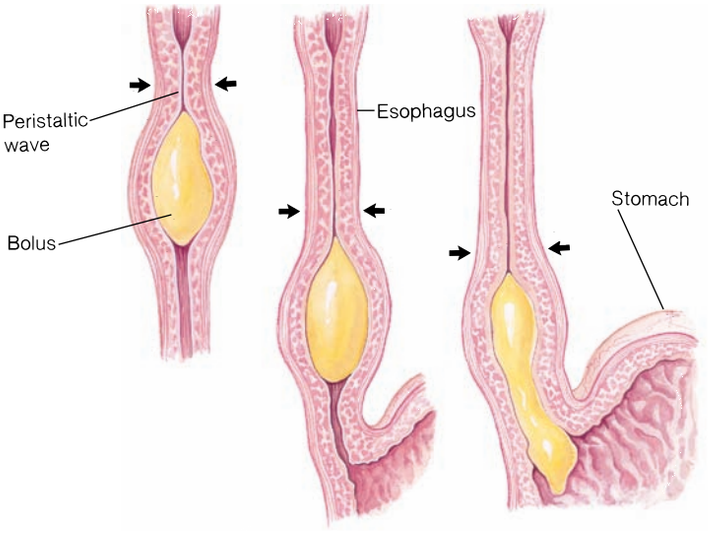

Figure 18.4 **Peristalsis in the esophagus.** Peristaltic contraction and movement of a bolus into the stomach.

The lumen of the terminal portion of the esophagus is slightly narrowed because of a thickening of the circular muscle fibers in its wall. This portion is referred to as the **lower esophageal (gastroesophageal) sphincter.** After food passes into the stomach, constriction of the muscle fibers of this region help prevent the stomach contents from regurgitating into the esophagus. Regurgitation would occur because the pressure in the abdominal cavity is greater than the pressure in the thoracic cavity as a result of respiratory movements. The lower esophageal sphincter must therefore remain closed until food is pushed through it by peristalsis into the stomach.

CLINICAL APPLICATION

The lower esophageal sphincter is not a true sphincter muscle that can be identified histologically, and it does at times permit the acidic contents of the stomach to enter the esophagus. This can create a burning sensation commonly called **heartburn,** although the heart is not involved. In infants under a year of age the lower esophageal sphincter may function erratically, causing them to "spit up" following meals. Certain mammals, such as rodents, have a true gastroesophageal sphincter and thus cannot regurgitate. This is why poison grains are effective in killing mice and rats.

Stomach

The J-shaped **stomach** is the most distensible part of the GI tract. It is continuous with the esophagus superiorly and empties into the duodenum of the small intestine inferiorly. The functions of the stomach are to store food, to initiate the digestion of proteins, to kill bacteria with the strong acidity of gastric juice, and to move the food into the small intestine as a pasty material called **chyme.**

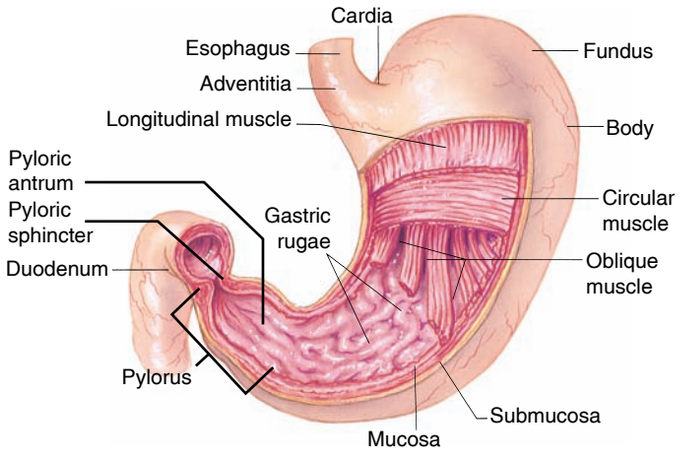

Figure 18.5 **Primary regions and structures of the stomach.** Notice that the pyloric region of the stomach includes the pyloric antrum (the wider portion of the pylorus) as well as the pyloric sphincter.

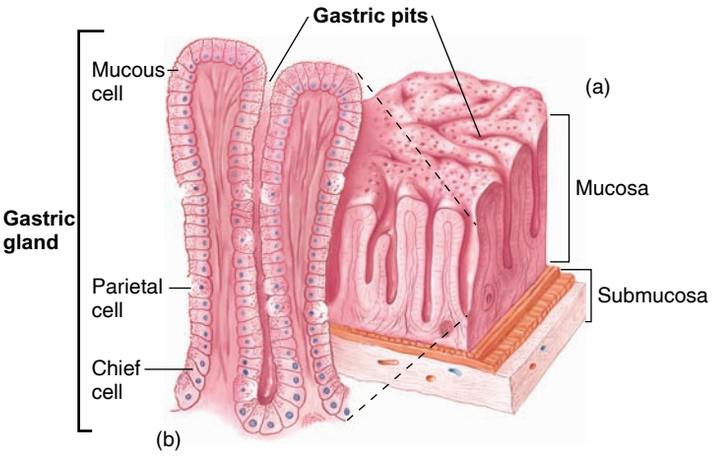

Figure 18.6 **Gastric pits and gastric glands of the mucosa.** (*a*) Gastric pits are the openings of the gastric glands. (*b*) Gastric glands consist of several types of cells (including mucous cells, chief cells, and parietal cells), each of which produces a specific secretion.

Swallowed food is delivered from the esophagus to the *cardiac region* of the stomach (fig. 18.5). An imaginary horizontal line drawn through the cardiac region divides the stomach into an upper *fundus* and a lower *body,* which together compose about two-thirds of the stomach. The distal portion of the stomach is called the *pyloric region.* The pyloric region begins in a somewhat widened area, the *antrum,* and ends at the *pyloric sphincter.* Contractions of the stomach churn the chyme, mixing it more thoroughly with the gastric secretions. These contractions also push partially digested food from the antrum through the pyloric sphincter and into the first part of the small intestine.

The inner surface of the stomach is thrown into long folds called *rugae,* which can be seen with the unaided eye. Microscopic examination of the gastric mucosa shows that it is likewise folded. The openings of these folds into the stomach lumen are called **gastric pits.** The cells that line the folds secrete various products into the stomach; these cells form the exocrine **gastric glands** (fig. 18.6).

Gastric glands contain several types of cells that secrete different products:

1. **mucous neck cells,** which secrete mucus (these supplement the surface mucous cells, which line the luminal surface of the stomach and the gastric pits).
2. **parietal cells,** which secrete *hydrochloric acid (HCl);*
3. **chief** (or **zymogenic**) **cells,** which secrete *pepsinogen,* an inactive form of the protein-digesting enzyme *pepsin;*
4. **enterochromaffin-like (ECL) cells,** found in the stomach and intestine, which secrete *histamine* and *5-hydroxytryptamine* (also called *serotonin*) as paracrine regulators of the GI tract;
5. **G cells,** which secrete the hormone *gastrin* into the blood; and
6. **D cells,** which secrete the hormone *somatostatin.*

In addition to these products, the gastric mucosa (probably the parietal cells) secretes a polypeptide called **intrinsic factor,** which is required for the intestinal absorption of vitamin B_{12}. Vitamin B_{12} is necessary for the production of red blood cells in the bone marrow (see the next Clinical Application box). Also, the stomach has recently been shown to secrete a hormone named **ghrelin.** Secretion of this newly discovered hormone rises before meals and falls after meals. This may serve as a signal from the stomach to the brain that helps regulate hunger (chapter 19, section 19.2).

The exocrine secretions of the gastric cells, together with a large amount of water (2 to 4 L/day), form a highly acidic solution known as **gastric juice.**

CLINICAL APPLICATION

The only stomach function that appears to be essential for life is the secretion of *intrinsic factor.* This polypeptide is needed for the absorption of vitamin B_{12} in the terminal portion of the ileum in the small intestine, and vitamin B_{12} is required for maturation of red blood cells in the bone marrow. Following surgical removal of the stomach (gastrectomy) a patient has to receive B_{12} injections, or take B_{12} orally together with intrinsic factor. Without vitamin B_{12}, **pernicious anemia** will develop.

Pepsin and Hydrochloric Acid Secretion

The parietal cells secrete H^+, at a pH as low as 0.8, into the gastric lumen by primary active transport (involving carriers that function as an ATPase). These carriers, known as **H^+/K^+ ATPase pumps,** transport H^+ uphill against a million-to-one concentration gradient into the lumen of the stomach while they transport K^+ in the opposite direction (fig. 18.7).

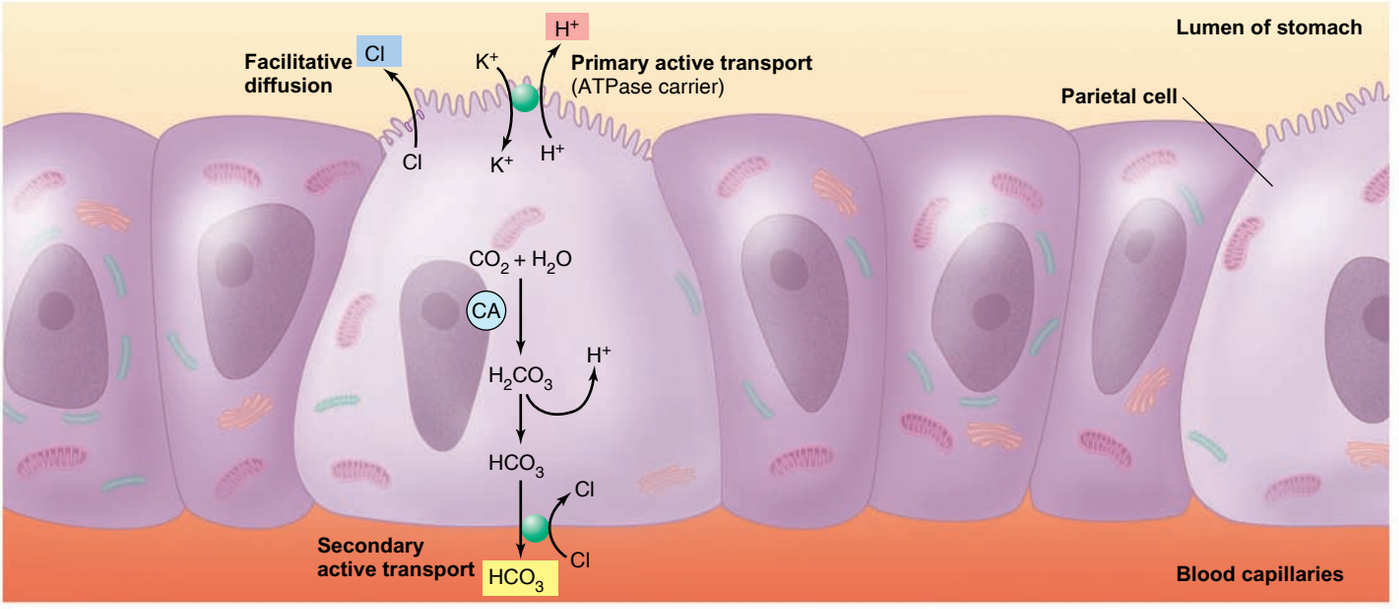

Figure 18.7 **Secretion of gastric acid by parietal cells.** The apical membrane (facing the lumen) secretes H^+ in exchange for K^+ using a primary active transport carrier that is powered by the hydrolysis of ATP. The basolateral membrane (facing the blood) secretes bicarbonate (HCO_3^-) in exchange for Cl^-. The Cl^- moves into the cell against its electrochemical gradient, powered by the downhill movement of HCO_3^- out of the cell. This HCO_3^- is produced by the dissociation of carbonic acid (H_2CO_3), which is formed from CO_2 and H_2O by the action of the enzyme carbonic anhydrase (abbreviated CA). The Cl^- then leaves the apical portion of the membrane by diffusion through a membrane channel. The parietal cells thus secrete HCl into the stomach lumen as they secrete HCO_3^- into the blood.

At the same time, the parietal cells' basolateral membranes (facing the blood in capillaries of the lamina propria) take in Cl^- against its electrochemical gradient by coupling its transport to the downhill movement of bicarbonate (HCO_3^-). The bicarbonate ion is produced within the parietal cells by the dissociation of carbonic acid, formed from CO_2 and H_2O by the enzyme carbonic anhydrase. Therefore, the parietal cells can secrete Cl^- (by facilitative diffusion) as well as H^+ into the gastric juice while they secrete bicarbonate into the blood (fig. 18.7).

The secretion of HCl by the parietal cells is stimulated by a variety of factors, including gastrin, histamine, and particular neurotransmitters. Gastrin, secreted by the G cells, is carried in the general circulation to the parietal cells, where it stimulates acid secretion. Gastrin also stimulates the ECL cells to secrete histamine, and histamine then acts as a paracrine regulator to stimulate HCl secretion by the parietal cells (see fig. 18.30). Histamine stimulation of parietal cells is mediated by the H_2 type of histamine receptor, which is different from the H_1 type of histamine receptor involved in allergic reactions (chapter 15). Parasympathetic neurons of the vagus nerve stimulate both parietal and ECL cells, although stimulation of ECL cells is believed to be the most important effect. This is particularly true at night during sleep, when the secretion of histamine from ECL cells is most responsible for stimulating gastric HCl secretion (see fig. 18.30). This is why drugs that block H_2 histamine receptors (such as Tagamet and Zantac) are more effective at night than they are at blocking meal-stimulated HCl secretion.

CLINICAL APPLICATION

Gastroesophageal reflux disease (**GERD**) is a common disorder in which the reflux of acidic gastric juice into the esophagus causes frequent heartburn or complications. GERD can be associated with laryngitis and cough, and can produce injuries to the esophagus that include *esophagitis* (producing erosions of the mucosa and ulcers), *stricture* of the lumen, *Barrett's esophagus* (columnar cells in place of the squamous epithelium), and *adenocarcinoma*. GERD can be reduced by lifestyle modifications (such as not eating at least 3 hours before going to bed), and is often treated with drugs that inhibit the H^+/K^+ pumps in the gastric mucosa. Such **proton pump inhibitors,** including Prilosec (omeprazole) and Prevacid (lansoprazole), are also used in the treatment of peptic ulcers. Because gastric acid secretion is stimulated by histamine from the ECL cells, acid secretion can also be reduced by drugs (such as Tagamet and Zantac) that block the H_2 histamine receptors in the gastric mucosa.

The high concentration of HCl from the parietal cells makes gastric juice very acidic, with a pH of less than 2. This strong acidity serves three functions:

1. Ingested proteins are denatured at low pH—that is, their tertiary structure (chapter 2) is altered so that they become more digestible.
2. Under acidic conditions, weak pepsinogen enzymes partially digest each other—this frees the fully active

pepsin enzyme as small inhibitory fragments are removed (fig. 18.8).

3. Pepsin is more active under acidic conditions—it has a pH optimum (chapter 4) of about 2.0.

As a result of the activation of pepsin under acidic conditions, the fully active pepsin is able to catalyze the hydrolysis of peptide bonds in the ingested protein. Thus, the cooperative activities of pepsin and HCl permit the partial digestion of food protein in the stomach.

The strong acid and protein-digesting action of pepsin could damage the lining of the stomach (produce a *peptic ulcer,* as described shortly). The first line of defense against such damage is a stable gel of mucus that is adherent (stuck) to the gastric epithelial surface. This **adherent layer of mucus** contains alkaline bicarbonate (HCO_3^-), secreted from the apical plasma membranes of the epithelial cells. When the stomach secretes more acid into the lumen, there is also more bicarbonate available to the epithelial cells for secretion into the mucus (see fig. 18.7). As a result, the pH at the epithelial surface is normally near neutral.

Also, the adherent layer of gastric mucus is the major barrier to potential damage to the stomach caused by pepsin. Little attention has historically been paid to pepsin's ability to cause damage, but there is evidence that it could pose a significant threat. Indeed, the damage to the esophagus caused by gastroesophageal reflux could be due more to pepsin than to acid. The adherent mucus layer in the stomach protects the gastric lining from pepsin by slowing its diffusion so that it doesn't normally reach the epithelial cells.

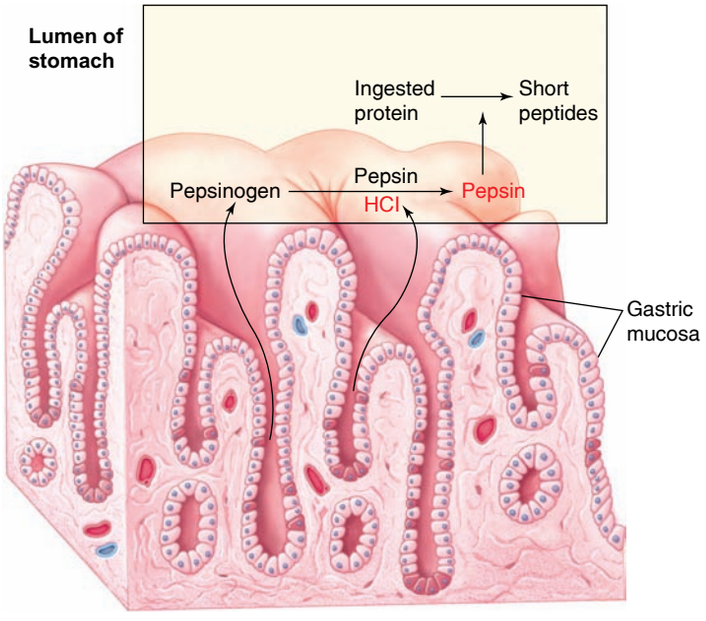

Figure 18.8 **The activation of pepsin.** The gastric mucosa secretes the inactive enzyme pepsinogen and hydrochloric acid (HCl). In the presence of HCl, the active enzyme pepsin is produced. Pepsin digests proteins into shorter polypeptides.

Although the adherent layer of alkaline mucus is the first line of defense against acid and pepsin damage to the stomach, there are other important protective mechanisms. These include the presence of tight junctions between adjacent epithelial cells, which prevent acid and pepsin from leaking past the epithelial barrier and destroying underlying tissues. Also, a rapid rate of epithelial cell division replaces the entire epithelium every 3 days, so that damaged cells can be rapidly replaced.

Digestion and Absorption in the Stomach

Proteins are only partially digested in the stomach by the action of pepsin, while carbohydrates and fats are not digested at all by pepsin. (Digestion of starch begins in the mouth with the action of salivary amylase and continues for a time when the food enters the stomach, but amylase soon becomes inactivated by the strong acidity of gastric juice.) The complete digestion of food molecules occurs later, when chyme enters the small intestine. Therefore, people who have had partial gastric resections—and even those who have had complete gastrectomies—can still adequately digest and absorb their food.

Almost all of the products of digestion are absorbed through the wall of the small intestine; the only commonly ingested substances that can be absorbed across the stomach wall are alcohol and aspirin. Absorption occurs as a result of the lipid solubility of these molecules. Aspirin and most other NSAIDs (nonsteroidal anti-inflammatory drugs) can promote damage to the gastric mucosa and cause bleeding, and must be avoided in people with gastric ulcers.

Gastritis and Peptic Ulcers

Peptic ulcers are erosions of the mucosa of the stomach or duodenum (produced by the action of HCl) that penetrate through the muscularis mucosa layer. In *Zollinger-Ellison syndrome,* ulcers of the duodenum are produced by excessive gastric acid secretion in response to very high levels of the hormone gastrin. Gastrin is normally secreted by the stomach, but in this case it is released by a gastrin-secreting tumor that is usually located in the duodenum or pancreas. This is a rare condition, but it does demonstrate that excessive gastric acid can cause ulcers of the duodenum. Ulcers of the stomach, however, are not believed to be due to excessive acid secretion, but rather to mechanisms that reduce the barriers of the gastric mucosa to self-digestion.

It has been known for some time that most people who have peptic ulcers are infected with a bacterium known as *Helicobacter pylori,* which resides in the gastrointestinal tract of almost half the adult population worldwide. The 2005 Nobel Prize in Physiology or Medicine was awarded to two scientists who discovered that this common bacterium, rather than emotional stress or spicy food, is the cause of most cases of peptic ulcers of the stomach and duodenum. As a result of this discovery, ulcers can now be effectively

treated medically with a drug regimen that consists of a *proton pump inhibitor* (a drug such as Prilosec that inhibits the K^+/H^+ pumps) combined with two different antibiotics (such as *amoxicillin* and *clarithromycin*) to suppress the *H. pylori* infection.

Prostaglandins produced by the gastric mucosa stimulate mucus and bicarbonate production and contribute to the formation of the mucosal barrier. Because NSAIDs (nonsteroidal anti-inflammatory drugs, such as aspirin) inhibit prostaglandin production, these drugs can damage the gastric mucosa. When the gastric barriers to self-digestion are broken down, acid can leak through the mucosa to the submucosa, causing direct damage and stimulating inflammation. The histamine released from mast cells during inflammation may stimulate further acid secretion (see fig. 18.30) and result in further damage to the mucosa. The inflammation that occurs during these events is called **acute gastritis.** This is why drugs that block the H_2 histamine receptors (such as Tagamet and Zantac) may be used to treat the gastritis.

The duodenum is normally protected from gastric acid by the adherent layer of mucus on its epithelium. Duodenal cells secrete bicarbonate into this adherent mucus layer, so that the surface epithelium is normally exposed to a neutral pH. Additional protection against gastric acid is provided through bicarbonate secreted by Brunner's glands in the submucosa, which are glands unique to the duodenum. Finally, the acidic chyme is neutralized by the buffering action of bicarbonate in alkaline pancreatic juice, which is released into the duodenum upon the arrival of the acidic chyme from the stomach. Duodenal ulcers may result from excessive gastric acid secretion and/or inadequate secretion of bicarbonate in the duodenum. Indeed, some studies have demonstrated that people with duodenal ulcers have a reduced secretion of duodenal bicarbonate in response to acid in the lumen.

People with gastritis and peptic ulcers should avoid substances that stimulate acid secretion, including coffee and alcohol, and often must take antacids (such as Tums), H_2-histamine receptor blockers (such as Zantac), or proton pump inhibitors (such as Prilosec). If the cause is excessive activity of *Helicobacter pylori,* antibiotics may also be required.

Case Investigation CLUES

Alan had a sharp pain in his stomach whenever he drank wine.

- What may be responsible for Alan's pain?
- What medicine might help alleviate this pain, and how would it work?

CHECKPOINT

4. Describe the structure and function of the lower esophageal sphincter.
5. List the secretory cells of the gastric mucosa and the products they secrete.
6. Describe the functions of hydrochloric acid in the stomach.
7. Explain how peptic ulcers are produced and why they are more likely to occur in the duodenum than in the stomach.
8. Explain how gastrin and vagus nerve stimulation cause the parietal cells to secrete HCl.

18.3 SMALL INTESTINE

The mucosa of the small intestine is folded into villi that project into the lumen. In addition, the cells that line these villi have foldings of their plasma membrane called microvilli. This arrangement greatly increases the surface area for absorption and improves digestion, since digestive enzymes are embedded within the microvilli.

LEARNING OUTCOMES

After studying this section, you should be able to:

- Describe the structure and functions of the small intestine
- Identify the location and describe the functions of the digestive enzymes of the small intestine

The **small intestine** (fig. 18.9) is that portion of the GI tract between the pyloric sphincter of the stomach and the ileocecal valve opening into the large intestine. It is called "small" because of its relatively small diameter compared to that of the large intestine. The small intestine is the longest part of the GI tract, however. It is approximately 3 m (12 ft) long in a living person, but it will measure nearly twice this length in a cadaver when the muscle wall is relaxed. The first 20 to 30 cm (10 in.) extending from the pyloric sphincter is the **duodenum.** The next two-fifths of the small intestine is the **jejunum,** and the last three-fifths is the **ileum.** The ileum empties into the large intestine through the ileocecal valve.

The products of digestion are absorbed across the epithelial lining of the intestinal mucosa. Absorption of carbohydrates, lipids, amino acids, calcium, and iron occurs primarily in the duodenum and jejunum. Bile salts, vitamin B_{12}, water, and electrolytes are absorbed primarily in the ileum. Absorption occurs at a rapid rate as a result of extensive foldings of the intestinal mucosa, which greatly increase its absorptive surface area. The mucosa and submucosa form large folds called *plicae circulares,* which can be observed with the unaided eye. The surface area is further increased

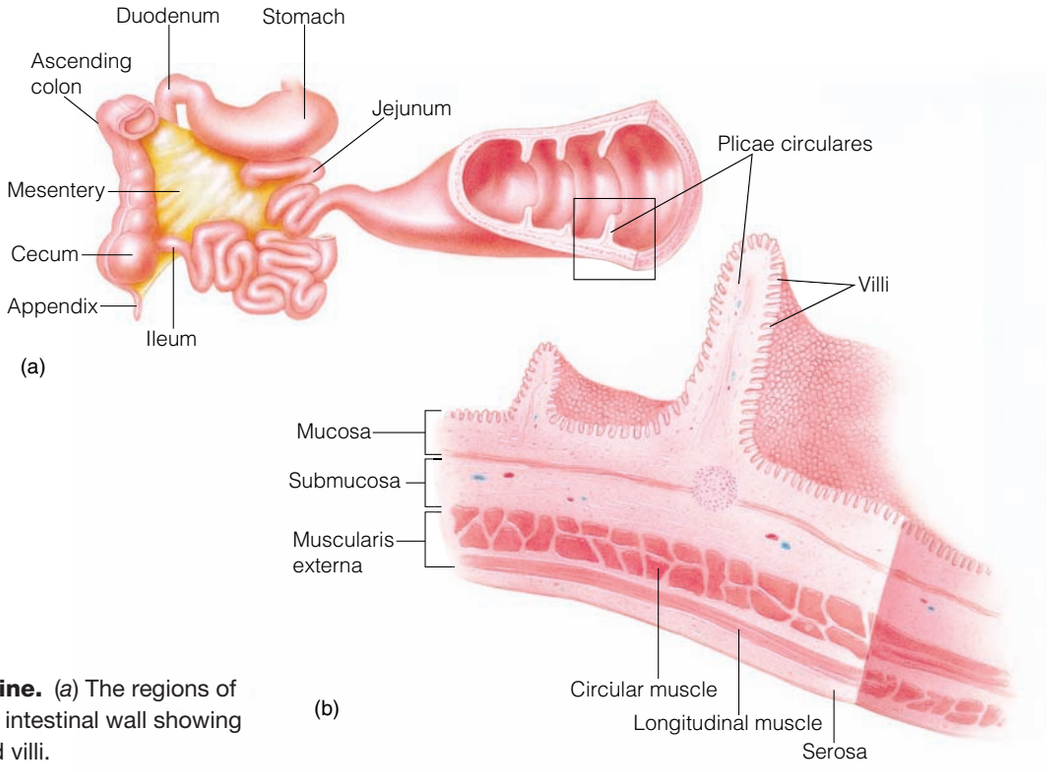

Figure 18.9 **The small intestine.** (*a*) The regions of the small intestine. (*b*) A section of the intestinal wall showing the tissue layers, plicae circulares, and villi.

by microscopic folds of mucosa called *villi,* and by foldings of the apical plasma membrane of epithelial cells (which can be seen only with an electron microscope) called *microvilli.*

Villi and Microvilli

Each **villus** is a fingerlike fold of mucosa that projects into the intestinal lumen (fig. 18.10). The villi are covered with columnar epithelial cells, among which are interspersed mucus-secreting *goblet cells.* The lamina propria, which forms the connective tissue core of each villus, contains numerous lymphocytes, blood capillaries, and a lymphatic vessel called the *central lacteal* (fig. 18.10). Absorbed monosaccharides and amino acids enter the blood capillaries; absorbed fat enters the central lacteals.

Epithelial cells at the tips of the villi are continuously exfoliated (shed) and are replaced by cells that are pushed up from the bases of the villi. The epithelium at the base of the villi invaginates downward to form narrow pouches that open through pores to the intestinal lumen. These structures are called **intestinal crypts,** or *crypts of Lieberkühn* (fig. 18.10).

The base of an intestinal crypt contains *Paneth cells,* which secrete antibacterial molecules (lysozyme and antimicrobial peptides) that may help to protect the intestine from inflammation. Also, each intestinal crypt contains several *stem cells,* which divide by mitosis to replenish themselves and to produce the differentiated cells of the intestinal mucosa. These newly formed cells migrate from the crypts to the tip of the villi, a journey of three days. Cells at the tips of the villi then undergo apoptosis and are shed into the lumen. In this way, the intestinal epithelium is renewed every four to five days.

Microvilli are formed by foldings at the apical surface of each epithelial cell membrane. These minute projections can be seen clearly only in an electron microscope. In a light microscope, the microvilli produce a somewhat vague **brush border** on the edges of the columnar epithelial cells. The terms *brush border* and *microvilli* are thus often used interchangeably in describing the small intestine (fig. 18.11).

Intestinal Enzymes

In addition to providing a large surface area for absorption, the plasma membranes of the microvilli contain digestive enzymes that hydrolyze disaccharides, polypeptides, and other substrates (table 18.1). These **brush border enzymes**

CLINICAL APPLICATION

The ability to digest milk sugar, or lactose, depends on the presence of a brush border enzyme called *lactase.* This enzyme is present in all children under the age of four but becomes inactive to some degree in most adults (people of Asian or African heritage are more often lactase deficient than Caucasians). A deficiency of lactase can result in **lactose intolerance,** a condition in which too much undigested lactose in the intestine causes diarrhea, gas, cramps, and other unpleasant symptoms. Yogurt is better tolerated than milk because it contains lactase (produced by the yogurt bacteria), which becomes activated in the duodenum and digests lactose.

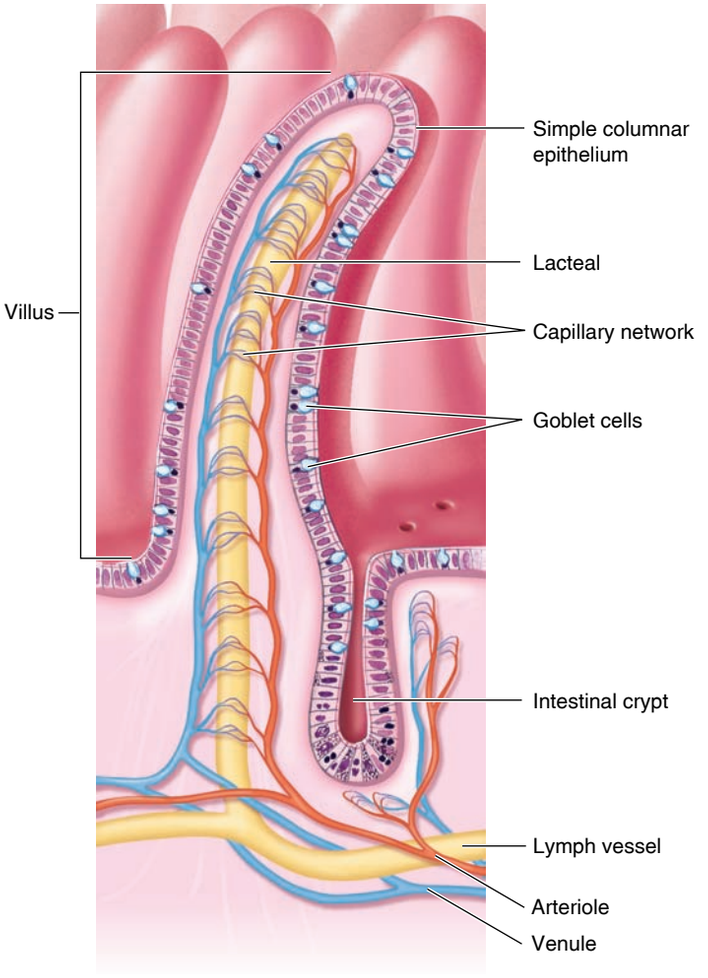

Figure 18.10 **The structure of an intestinal villus.** The figure also depicts an intestinal crypt (crypt of Lieberkühn), in which new epithelial cells are produced by mitosis.

are not secreted into the lumen, but instead remain attached to the plasma membrane with their active sites exposed to the chyme (fig. 18.12). One brush border enzyme, **enterokinase,** is required for activation of the protein-digesting enzyme *trypsin,* which enters the small intestine in pancreatic juice.

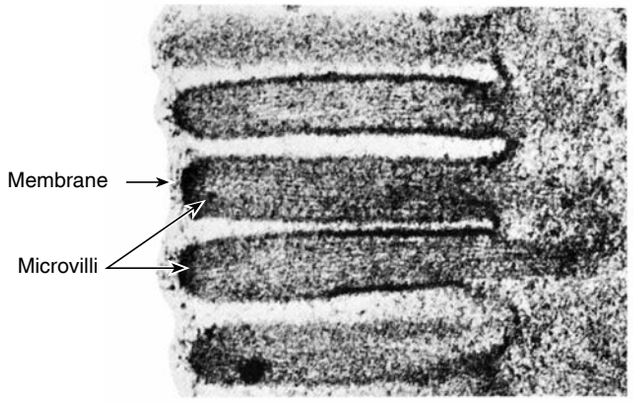

Figure 18.11 **Electron micrograph of microvilli.** Microvilli are evident at the apical surface of the columnar epithelial cells in the small intestine. Microvilli increase the surface area for absorption and also have the brush border digestive enzymes embedded in their plasma membranes. From Keith R. Porter, D. H. Alpers, and D. Seetharan, "Pathophysiology of Diseases Involving Intestinal Brush-Border Proteins" in *New England Journal of Medicine,* Vol. 296, 1977, p. 1047, fig. 1. Copyright © 1977 Massachusetts Medical Society. All rights reserved.

Intestinal Contractions and Motility

Two major types of contractions occur in the small intestine: *peristalsis* and *segmentation.* Peristalsis is much weaker in the small intestine than in the esophagus and stomach. Intestinal motility—the movement of chyme through the intestine—is relatively slow and is due primarily to the greater pressure at the pyloric end of the small intestine than at the distal end.

The major contractile activity of the small intestine is **segmentation.** This term refers to muscular constrictions of the lumen, which occur simultaneously at different intestinal segments (fig. 18.13). This action serves to mix the chyme more thoroughly. Segmentation contractions occur more frequently in the proximal than in the distal end of the intestine, producing the pressure difference mentioned earlier and helping to move chyme through the small intestine.

Table 18.1 | Brush Border Enzymes Attached to the Cell Membrane of Microvilli in the Small Intestine

Category	Enzyme	Comments
Disaccharidase	Sucrase	Digests sucrose to glucose and fructose; deficiency produces gastrointestinal disturbances
	Maltase	Digests maltose to glucose
	Lactase	Digests lactose to glucose and galactose; deficiency produces gastrointestinal disturbances (lactose intolerance)
Peptidase	Aminopeptidase	Produces free amino acids, dipeptides, and tripeptides
	Enterokinase	Activates trypsin (and indirectly other pancreatic juice enzymes); deficiency results in protein malnutrition
Phosphatase	Ca^{2+}, Mg^{2+}-ATPase	Needed for absorption of dietary calcium; enzyme activity regulated by vitamin D
	Alkaline phosphatase	Removes phosphate groups from organic molecules; enzyme activity may be regulated by vitamin D

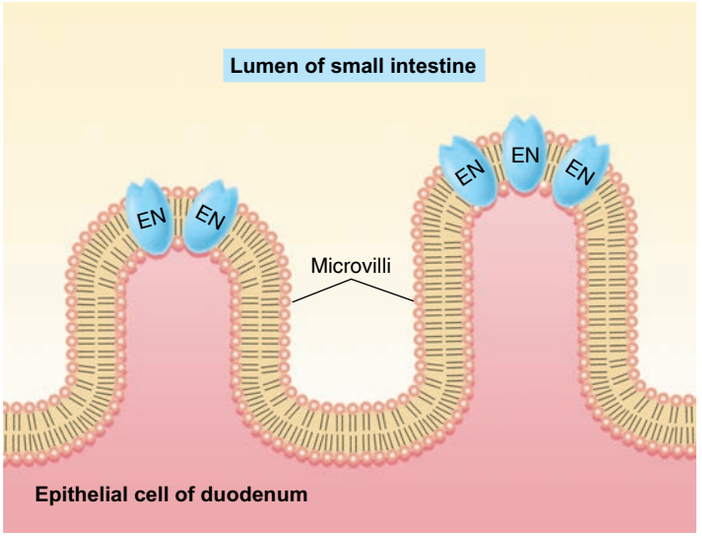

Figure 18.12 **Location of brush border enzymes.** The brush border enzymes (EN) are embedded in the plasma membrane of the microvilli in the small intestine. The active sites of these enzymes face the chyme in the lumen, helping to complete the digestion of food molecules.

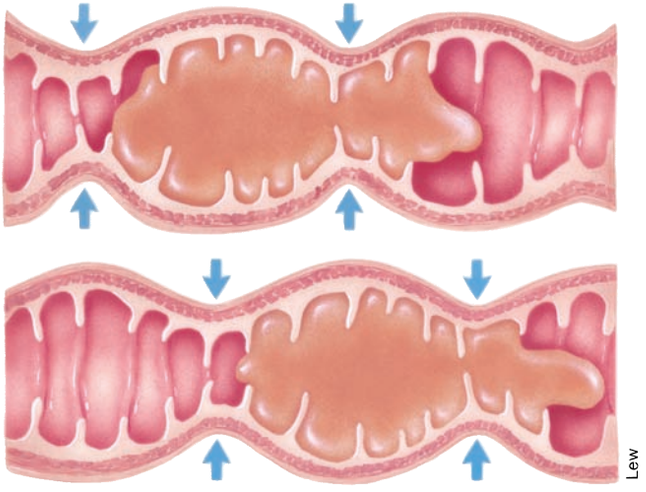

Figure 18.13 **Segmentation of the small intestine.** Simultaneous contractions of numerous segments of the intestine help mix the chyme with digestive enzymes and mucus.

Contractions of intestinal smooth muscles occur automatically in response to endogenous pacemaker activity, somewhat analogous to the automatic beating of the heart. In intestinal smooth muscle, however, the rhythm of contractions is paced by graded depolarizations called **slow waves** (fig. 18.14). The slow waves are produced by unique cells, often associated with autonomic nerve endings. However, these pacemaker cells are neither neurons nor smooth muscle cells; they are the cells identified histologically as the **interstitial cells of Cajal.** These compose about 5% of the cells in the muscularis layer, and have long processes

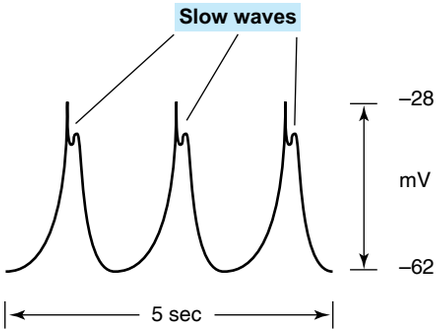

Figure 18.14 **Slow waves in the intestine.** The slow waves are produced by the interstitial cells of Cajal (ICC), not by smooth muscle cells, and are apparently conducted by networks of ICC that are electrically joined together within the intestinal wall. Smooth muscle cells respond to this depolarization by producing action potentials and contracting. Note that the slow waves occur much slower (with a rate measured in seconds) than do the pacemaker potentials in the heart.

that join different interstitial cells of Cajal to each other and to smooth muscle cells by gap junctions. The gap junctions permit the spread of depolarization from one cell to the next (fig. 18.15).

Slow waves spread by way of gap junctions between the interconnected cells of Cajal in the stomach and intestines. However, the slow waves can spread only a short distance (a few centimeters) and thus must be regenerated by the next pacemaker region. This produces the segmentation contractions of the intestine (see fig. 18.13). The production of slow waves, and resulting contractions, are faster at the proximal end of the intestine than at the distal end, so that there is a pressure head that pushes the intestinal contents along the GI tract.

The slow waves produced and conducted by the interstitial cells of Cajal serve to depolarize the adjacent smooth muscle cells. When the slow-wave depolarization exceeds a threshold value, it triggers action potentials in the smooth muscle cells by opening voltage-gated Ca^{2+} channels. The inward flow of Ca^{2+} has two effects: (1) it produces the upward depolarization phase of the action potential (repolarization is produced by outward flow of K^{+}); and (2) it stimulates contraction (as described in chapter 12; see fig. 12.36). Contraction may then be aided by additional calcium released from the sarcoplasmic reticulum through calcium-induced calcium release.

Autonomic nerves modify the automatic contractions of the intestine largely by influencing the enteric nervous system (section 18.6; see fig. 18.31), which in turn stimulates or inhibits the interstitial cells of Cajal. Acetylcholine, released by postganglionic axons and acting through muscarinic receptors, increases the amplitude and duration of the slow waves. Thus, it increases the production of action potentials and promotes contractions and motility of the intestine.

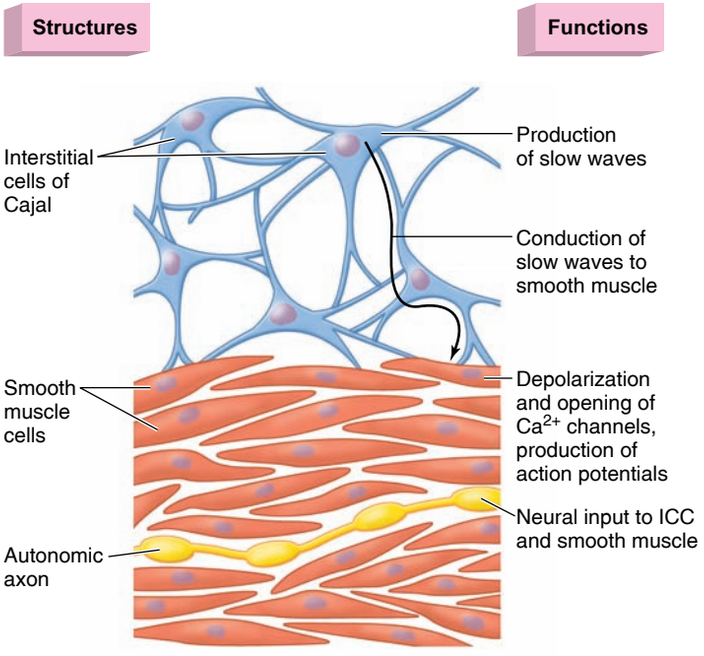

Figure 18.15 Cells responsible for the electrical events within the muscularis. The interstitial cells of Cajal (ICC) generate the slow waves, which pace the contractions of the intestine. Slow waves are conducted into the smooth muscle cells where they can stimulate opening of Ca^{2+} channels. This produces action potentials and stimulates contraction. Autonomic axons have varicosities that release neurotransmitters, which modify the inherent electrical activity of the interstitial cells of Cajal and smooth muscle cells.

✔ CHECKPOINT

9. Describe the structures that increase the surface area of the small intestine, and explain the function of the intestinal crypts.
10. Explain what is meant by the term *brush border,* and give some examples of brush border enzymes. Why is it that many adults cannot tolerate milk?
11. Explain how smooth muscle contraction in the small intestine is regulated. What is the function of segmentation?

18.4 LARGE INTESTINE

The large intestine absorbs water, electrolytes, and certain vitamins from the chyme it receives from the small intestine. The large intestine then passes waste products out of the body through the rectum and anal canal.

LEARNING OUTCOMES

After studying this section, you should be able to:

- ✔ Describe the structure and functions of the large intestine
- ✔ Explain the nature and significance of the intestinal microbiota

The **large intestine,** or **colon,** extends from the ileocecal valve to the anus, framing the small intestine on three sides. Chyme from the ileum passes into the **cecum,** which is a blind pouch (open only at one end) at the beginning of the large intestine. Waste material then passes in sequence through the **ascending colon, transverse colon, descending colon, sigmoid colon, rectum,** and **anal canal** (fig. 18.16). Waste material (feces) is excreted through the *anus,* the external opening of the anal canal.

The mucosa of the large intestine, like that of the small intestine, contains many scattered lymphocytes and lymphatic nodules and is covered by columnar epithelial cells and mucus-secreting goblet cells. Although this epithelium does form crypts (fig. 18.17), there are no villi in the large intestine—the intestinal mucosa therefore appears flat. The outer surface of the colon bulges outward to form pouches, or **haustra** (figs. 18.16 and 18.18). Occasionally, the muscularis externa of the haustra may become so weakened that the wall forms a more elongated outpouching, or diverticulum (*divert* = turned aside). Inflammation of one or more of these structures is called *diverticulitis.* The large intestine has little or no digestive function, but it does absorb water and electrolytes from the remaining chyme, as well as several B complex vitamins and vitamin K.

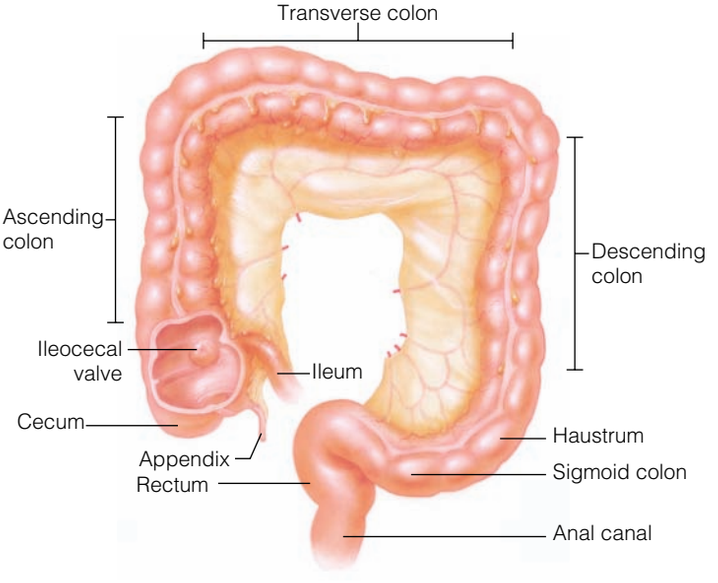

Figure 18.16 The large intestine. The different regions of the large intestine (colon) are illustrated.

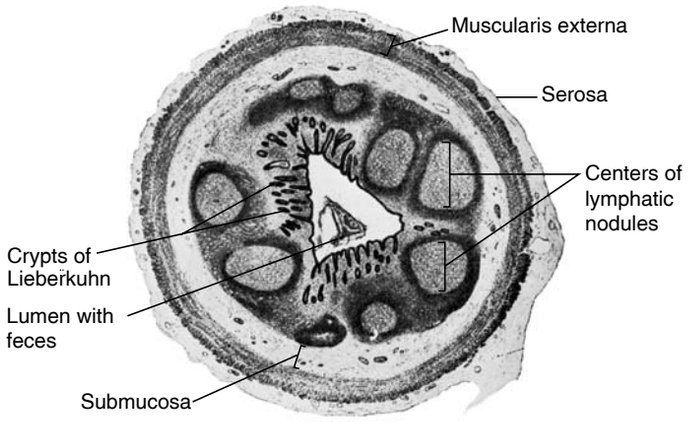

Figure 18.17 A photomicrograph of the human appendix. This cross section reveals numerous lymphatic nodules, which function in immunity.

CLINICAL APPLICATION

The *appendix* is a short, thin outpouching of the cecum. It does not function in digestion, but like the tonsils, it contains numerous lymphatic nodules (see fig. 18.17) and is subject to inflammation—a condition called **appendicitis.** This is commonly detected in its later stages by pain in the lower right quadrant of the abdomen. If the appendix ruptures, infectious material can spread throughout the surrounding body cavity, causing inflammation of the peritoneum—*peritonitis.* This dangerous event may be prevented by surgical removal of the inflamed appendix (*appendectomy*).

Case Investigation CLUE

Alan's pains were not present unless he ate particular foods or drank wine. He did not have a fever or an elevated white blood cell count.

- Do Alan's symptoms indicate appendicitis? Why or why not?

Intestinal Microbiota

Microorganisms, primarily bacteria, are present in relatively small numbers in the stomach and proximal portion of the small intestine. Their numbers increase in the distal ileum and are greatest in the colon, where an estimated 10^{14} reside. This enormous number is about 10 times more than the number of human cells in the body and represents several hundred different species with perhaps 100 times more genes than in human cells. These microorganisms are known collectively as the **intestinal microbiota** or **microflora.** In the colon, the intestinal microbiota are comprised mostly of anaerobic bacterial species.

Figure 18.18 A radiograph of the large intestine. The large intestine is seen after a barium enema has been administered; the haustra are clearly visible.

The microbiota are usually described as composed of **commensal bacteria;** *commensalism* refers to a relationship where one species benefits and the other is neither benefited nor harmed. However, *mutualism* may better describe the relationship between the intestinal microbiota and their human hosts; in mutualism, both species benefit. We provide the bacteria with nutrients and an anaerobic home in our large intestine; they provide us with a variety of benefits.

This intestinal microbiota originates at birth and performs a number of physiologically important functions. In addition to the production of B vitamins and vitamin K, bacteria in the colon ferment (through anaerobic metabolism) some indigestible molecules in the chyme and secreted mucus. They produce *short-chain fatty acids* (less than five carbons long), which are used for energy by the epithelial cells of the colon, and which aid the absorption of sodium, bicarbonate, calcium, magnesium, and iron in the large intestine. Scientists estimate that the short-chain fatty acids produced by our intestinal microbiota account for 10% of the calories in the average Western diet.

The correct balance of the bacterial species in the microbiota reduces the ability of pathogenic species to cause damage and produce such symptoms as diarrhea. Although the intestinal mucosa is an effective first-line immune barrier, some pathogenic bacteria can get through the mucosa,

and sometimes also through the mesenteric lymph nodes, to cause an inflammation. In contrast, the commensal bacteria are normally prevented from causing an inflammation by the innate and adaptive immune system. Intestinal dendritic cells, a type of antigen-presenting cell needed for the activation of T lymphocytes, activate regulatory T cells to suppress inflammation in response to commensal bacteria, while stimulating helper and cytotoxic T cells to combat pathogenic bacteria (chapter 15, section 15.3). These and other responses of the adaptive and innate immune system to commensal bacteria help to prevent inappropriate inflammatory responses in the gut and to protect the intestinal epithelium from injury.

The epithelial layer of the intestine is only about 20 μm across; this presents a thin barrier of high surface area to separate deeper tissues from the toxins and intestinal bacteria in the lumen that could provoke inflammation. A normal population of commensal bacteria is needed to limit the inflammation caused by pathogenic bacteria and to instigate proper repair of a damaged epithelium. On this basis, you might suppose that excessive use of antibiotics that reduces the normal population of commensal bacteria could lead to inflammatory damage of the intestine. Indeed, there is a rising incidence of **inflammatory bowel disease**—disorders involving chronic intestinal inflammation, including *Crohn's disease* and *ulcerative colitis*—associated with the increased use of antibiotics in the United States. Those with a genetic susceptibility, particularly to Crohn's disease, are most vulnerable.

Fluid and Electrolyte Absorption in the Intestine

Most of the fluid and electrolytes in the lumen of the GI tract are absorbed by the small intestine. Although a person may drink only about 1.5 L of water per day, the small intestine receives 7 to 9 L per day as a result of the fluid secreted into the GI tract by the salivary glands, stomach, pancreas, liver, and gallbladder. The small intestine absorbs most of this fluid and passes 1.5 to 2.0 L of fluid per day to the large intestine. The large intestine absorbs about 90% of this remaining volume, leaving less than 200 ml of fluid to be excreted in the feces.

Absorption of water in the intestine occurs passively as a result of the osmotic gradient created by the active transport of ions. The epithelial cells of the intestinal mucosa are joined together much like those of the kidney tubules and, like the kidney tubules, contain Na^+/K^+ pumps in the basolateral membrane. The analogy with kidney tubules is emphasized by the observation that aldosterone, which stimulates salt and water reabsorption in the renal tubules, also appears to stimulate salt and water absorption in the ileum.

The handling of salt and water transport in the large intestine is made more complex by the ability of the large intestine to secrete, as well as absorb, water. The secretion of water by the mucosa of the large intestine occurs by osmosis as a result of the active transport of Na^+ or Cl^- out of the epithelial cells into the intestinal lumen. Secretion in this way is normally minor compared to the far greater amount of salt and water absorption, but this balance may be altered in some disease states.

CLINICAL APPLICATION

Diarrhea is characterized by excessive fluid excretion in the feces. Three different mechanisms, illustrated by three different diseases, can cause diarrhea. In *cholera,* severe diarrhea and dehydration result from *enterotoxin,* a chemical produced by the infecting bacteria. Release of enterotoxin stimulates active NaCl transport into the lumen of the intestine, followed by the osmotic movement of water. In *celiac sprue,* diarrhea is caused by damage to the intestinal mucosa produced in susceptible people by eating foods that contain gluten (proteins from grains such as wheat). In *lactose intolerance,* diarrhea is produced by the increased osmotic pressure in the intestinal lumen as a result of the presence of undigested lactose.

Defecation

After electrolytes and water have been absorbed the waste material that is left passes to the rectum, leading to an increase in rectal pressure, relaxation of the internal anal sphincter, and the urge to defecate. If the urge to defecate is denied, feces are prevented from entering the anal canal by the external anal sphincter. In this case the feces remain in the rectum, and may even back up into the sigmoid colon. The **defecation reflex** normally occurs when the rectal pressure rises to a particular level that is determined, to a large degree, by habit. At this point the external anal sphincter relaxes to admit feces into the anal canal.

During the act of defecation the longitudinal rectal muscles contract to increase rectal pressure, and the internal and external anal sphincter muscles relax. Excretion is aided by contractions of abdominal and pelvic skeletal muscles, which raise the intra-abdominal pressure (this is part of Valsalva's maneuver; chapter 14, section 14.6). The raised pressure helps push the feces from the rectum, through the anal canal, and out of the anus.

CHECKPOINT

12. Describe how electrolytes and water are absorbed in the large intestine, and explain how diarrhea may be produced.

13. Identify the nature and significance of the intestinal microflora.

14. Describe the structures and mechanisms involved in defecation.

18.5 LIVER, GALLBLADDER, AND PANCREAS

The liver regulates the chemical composition of the blood in numerous ways. In addition, the liver produces and secretes bile, which is stored and concentrated in the gallbladder prior to its discharge into the duodenum. The pancreas produces pancreatic juice, an exocrine secretion containing bicarbonate and important digestive enzymes.

LEARNING OUTCOMES

After studying this section, you should be able to:

- ✔ Describe the structure and functions of the liver
- ✔ Explain the synthesis, composition, and functions of bile
- ✔ Describe the composition of pancreatic juice and explain the significance of pancreatic juice enzymes

The *liver* is positioned immediately beneath the diaphragm in the abdominal cavity. It is the largest internal organ, weighing about 1.3 kg (3.5 to 4.0 lb) in an adult. Attached to the inferior surface of the liver, between its right and quadrate lobes, is the pear-shaped *gallbladder.* This organ is approximately 7 to 10 cm (3 to 4 in.) long. The *pancreas,* which is about 12 to 15 cm (5 to 6 in.) long, is located behind the stomach along the posterior abdominal wall.

Structure of the Liver

Although the liver is the largest internal organ, it is, in a sense, only one to two cells thick. This is because the liver cells, or **hepatocytes,** form **hepatic plates** that are one to two cells thick. The plates are separated from each other by large capillary spaces called **sinusoids** (fig. 18.19).

The liver sinusoids are lined by endothelial cells with flattened processes and *fenestrae*—openings 150 to 175 nanometers in diameter that make the sinusoids very porous. Unlike the fenestrated capillaries of the kidneys and pancreas, the fenestrae of the hepatic sinusoids lack a diaphragm and a basement membrane. This makes the hepatic sinusoids much more permeable than other capillaries, even permitting the passage of plasma proteins with protein-bound nonpolar molecules, such as fat and cholesterol. The sinusoids also contain phagocytic *Kupffer cells,* which are part of the reticuloendothelial system (also called the mononuclear phagocyte system; chapter 15, section 15.1). The fenestrae, lack of a basement membrane, and plate structure of the liver allow intimate contact between the hepatocytes and the contents of the blood.

The liver has an amazing ability to regenerate itself. For example, if two-thirds of a rodent's liver is surgically removed, the remaining tissue will regenerate its original mass in one week. This regenerative ability is due not to stem cells, but rather to the mitotic division of the remaining hepatocytes. When the original mass is restored, cell division ceases. The same regenerative ability is seen when most toxins or infections cause the hepatocytes to die. For reasons not presently understood, hepatic damage due to alcohol abuse and viral hepatitis

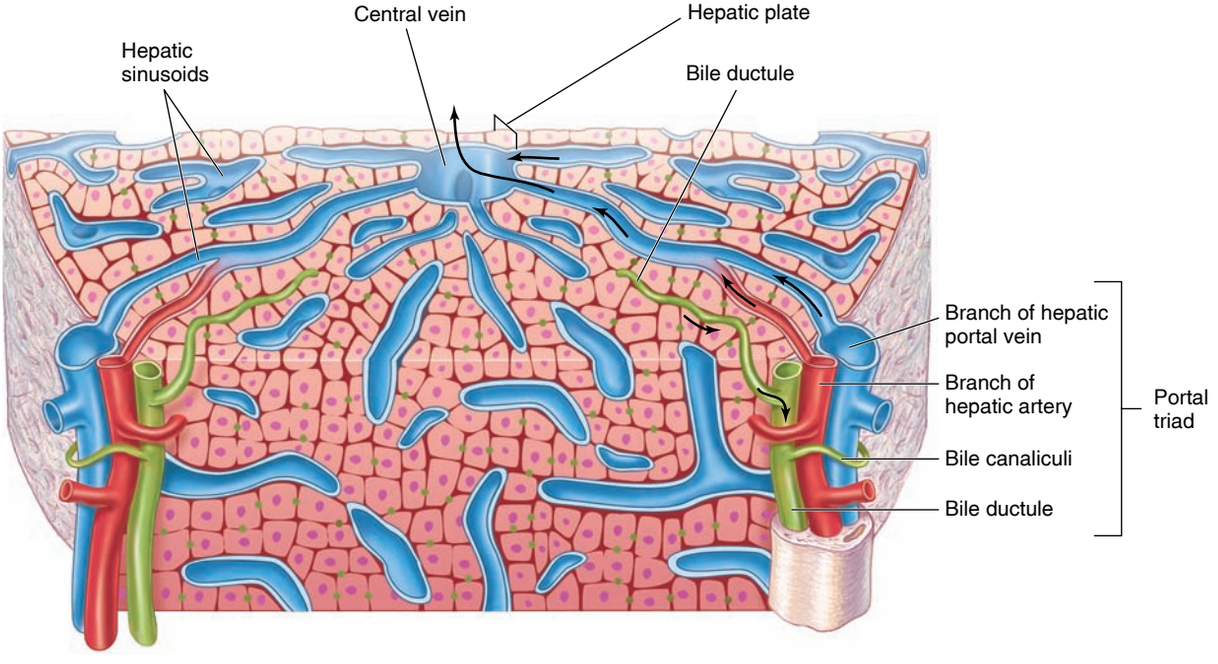

Figure 18.19 **Microscopic structure of the liver.** Blood enters a liver lobule through the vessels in a portal triad, passes through hepatic sinusoids, and leaves the lobule through a central vein. The central veins converge to form hepatic veins that transport venous blood from the liver.

can cause *liver fibrosis,* where there is accumulation of collagen fibers and extracellular matrix. This can lead to *cirrhosis,* a more serious condition described in the next Clinical Application box.

Hepatic Portal System

The products of digestion that are absorbed into blood capillaries in the intestine do not directly enter the general circulation. Instead, this blood is delivered first to the liver. Capillaries in the digestive tract drain into the *hepatic portal vein,* which carries this blood to capillaries in the liver. It is not until the blood has passed through this second capillary bed that it enters the general circulation through the *hepatic vein* that drains the liver. The term **portal system** is used to describe this unique pattern of circulation: capillaries ⇒ vein ⇒ capillaries ⇒ vein. In addition to receiving venous blood from the intestine, the liver also receives arterial blood via the *hepatic artery.*

The hepatic portal vein drains the capillaries of the intestine, pancreas, gallbladder, omentum, and spleen, and accounts for about 75% to 80% of the blood flow to the liver. Because it contains blood coming from the intestine, the hepatic portal vein delivers nutrients and other absorbed molecules to the liver. The hepatic artery supplies the remaining 20% to 25% of the liver's incoming blood flow; however, this arterial blood flow is adjusted to compensate for changes in the blood flow through the hepatic portal vein. As a result, the total hepatic blood flow is maintained at about 25% of the cardiac output. This relatively constant hepatic blood flow is needed to maintain *hepatic clearance*—the ability of the liver to remove substances from the blood, as will be described in the section on the enterohepatic circulation.

Liver Lobules

The hepatic plates are arranged into functional units called **liver lobules** (figs. 18.19 and 18.20). In the middle of each lobule is a *central vein,* and at the periphery of each lobule are branches of the hepatic portal vein and of the hepatic artery, which open into the sinusoids *between* hepatic plates. Arterial blood and portal venous blood, containing molecules absorbed in the GI tract, thus mix as the blood flows within the sinusoids from the periphery of the lobule to the central vein. The central veins of different liver lobules converge to form the hepatic vein, which carries blood from the liver to the inferior vena cava.

Bile is produced by the hepatocytes and secreted into thin channels called **bile canaliculi,** located *within* each hepatic plate (fig. 18.20). These bile canaliculi are drained at the periphery of each lobule by *bile ducts,* which in turn drain into *hepatic ducts* that carry bile away from the liver. Because blood travels in the sinusoids and bile travels in the opposite direction within the hepatic plates, blood and bile do not mix in the liver lobules.

Enterohepatic Circulation

In addition to the normal constituents of bile, a wide variety of exogenous compounds (drugs) are secreted by the liver into the bile ducts (table 18.2). The liver can thus "clear" the blood of particular compounds by removing them from the blood and excreting them into the intestine with the bile. Molecules that are cleared from the blood by secretion into the bile are eliminated in the feces; this is analogous to renal clearance of blood through excretion in the urine (chapter 17, section 17.4).

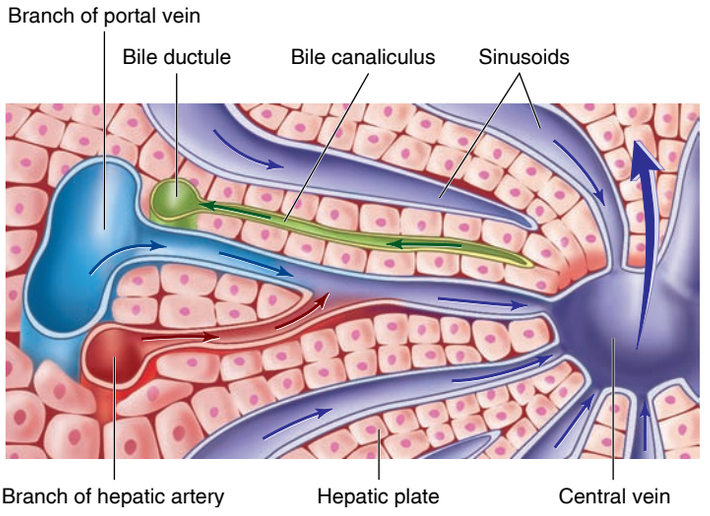

Figure 18.20 The flow of blood and bile in a liver lobule. Blood flows within sinusoids from a portal vein to the central vein (from the periphery to the center of a lobule). Bile flows within hepatic plates from the center to bile ductules at the periphery of a lobule.

CLINICAL APPLICATION

In **cirrhosis,** large numbers of liver lobules are destroyed by inflammatory processes and replaced with permanent, scarlike fibrotic connective tissue and "regenerative nodules" of hepatocytes. These regenerative nodules do not have the platelike structure of normal liver tissue, and are therefore less functional. One indication of this decreased function is the entry of ammonia (produced by intestinal bacteria) from the hepatic portal blood into the general circulation. Cirrhosis may be caused by chronic alcohol abuse, biliary obstruction, viral hepatitis, or various chemicals that attack liver cells.

Chronic alcohol abuse is the third leading preventable cause of death in the United States, due to its association with liver disease, several types of cancers, deaths from accidents and violence, and other causes that result in an average of 30 lost years per alcoholic death. The regular use of alcohol can cause **steatosis** (fatty liver), where hepatocytes store large globules of fat. This can progress to cirrhosis, with the incidence of cirrhosis increasing in proportion to the amount of alcohol consumed. Long-term alcohol abuse can also produce **alcoholic hepatitis,** a potentially fatal condition characterized by the rapid onset of jaundice (discussed shortly) and other symptoms.

Table 18.2 | Compounds Excreted by the Liver into the Bile Ducts

Category	Compound	Comments
Endogenous (Naturally occurring)	Bile salts, urobilinogen, cholesterol	High percentage reabsorbed and has an enterohepatic circulation*
	Lecithin	Small percentage reabsorbed and has an enterohepatic circulation
	Bilirubin	No enterohepatic circulation
Exogenous (Drugs)	Ampicillin, streptomycin, tetracyline	High percentage reabsorbed and has an enterohepatic circulation
	Sulfonamides, penicillin	Small percentage reabsorbed and has an enterohepatic circulation

*Compounds with an enterohepatic circulation are absorbed to some degree by the intestine and are returned to the liver in the hepatic portal vein.

Many compounds that are released with the bile into the intestine are not eliminated with the feces, however. Some of these can be absorbed through the small intestine and enter the hepatic portal blood. These molecules are thus carried back to the liver, where they can be again secreted by hepatocytes into the bile ducts. Compounds that recirculate between the liver and intestine in this way are said to have an **enterohepatic circulation** (fig. 18.21). For example, a few grams of bile salts (discussed shortly) released into the intestine recirculate 6 to 10 times a day, with only about 0.5 g of bile salts per day excreted in the feces.

Case Investigation CLUE

Alan's blood tests revealed normal levels of free bilirubin, ammonia, and urea.

- What do these results suggest about the health of Alan's liver?

Functions of the Liver

As a result of its large and diverse enzymatic content and its unique structure, and because it receives venous blood from the intestine, the liver has a greater variety of functions than any other organ in the body. The major categories of liver function are summarized in table 18.3.

Bile Production and Secretion

The liver produces and secretes 250 to 1,500 ml of bile per day. The major constituents of bile are *bile pigment (bilirubin), bile salts, phospholipids* (mainly lecithin), *cholesterol,* and *inorganic ions.*

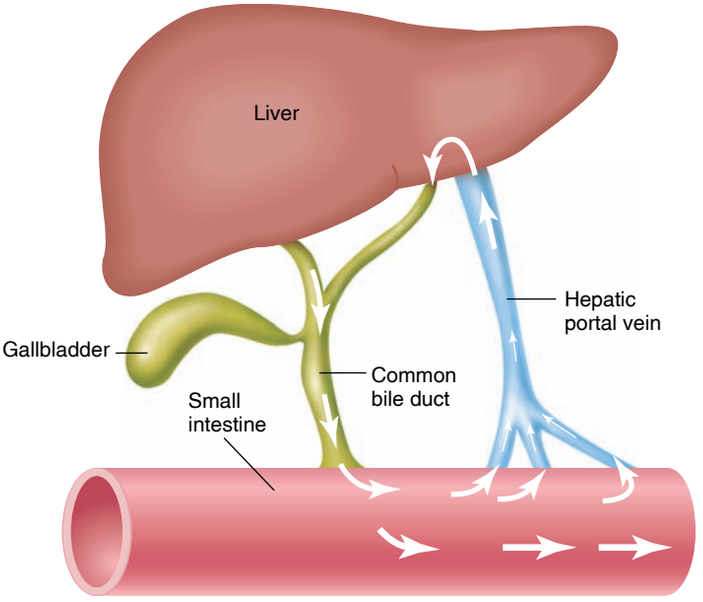

Figure 18.21 **The enterohepatic circulation.** Substances secreted in the bile may be absorbed by the intestinal epithelium and recycled to the liver via the hepatic portal vein.

Table 18.3 | Major Categories of Liver Function

Functional Category	Actions
Detoxication of Blood	Phagocytosis by Kupffer cells Chemical alteration of biologically active molecules (hormones and drugs) Production of urea, uric acid, and other molecules that are less toxic than parent compounds Excretion of molecules in bile
Carbohydrate Metabolism	Conversion of blood glucose to glycogen and fat Production of glucose from liver glycogen and from other molecules (amino acids, lactic acid) by gluconeogenesis Secretion of glucose into the blood
Lipid Metabolism	Synthesis of triglycerides and cholesterol Excretion of cholesterol in bile Production of ketone bodies from fatty acids
Protein Synthesis	Production of albumin Production of plasma transport proteins Production of clotting factors (fibrinogen, prothrombin, and others)
Secretion of Bile	Synthesis of bile salts Conjugation and excretion of bile pigment (bilirubin)

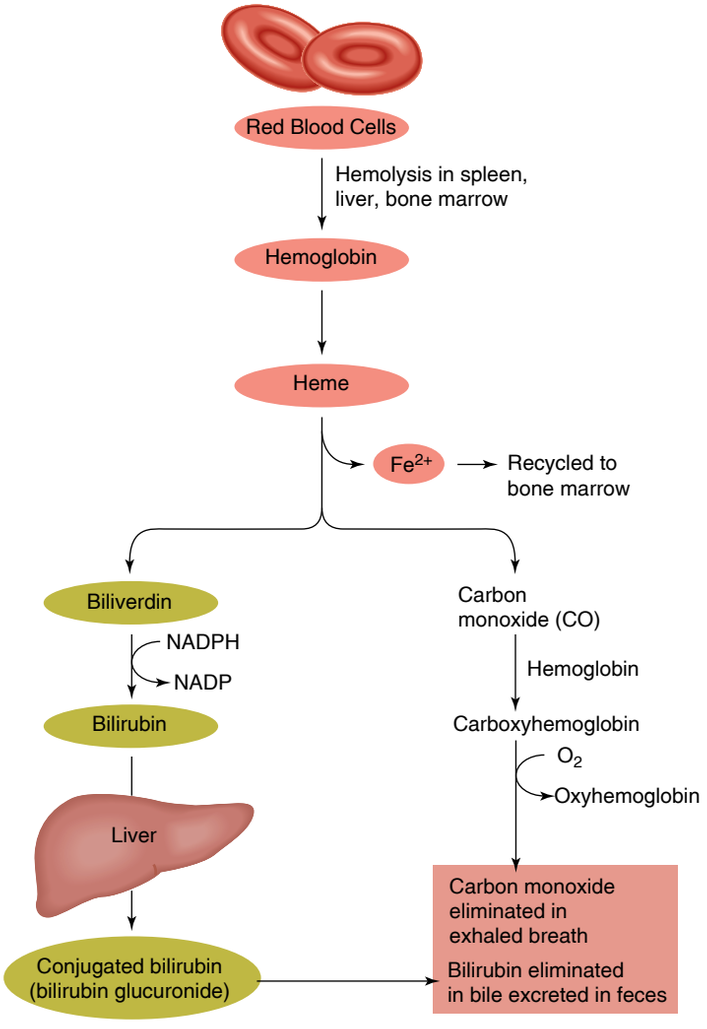

Figure 18.22 Simplified pathway for the metabolism of heme and bilirubin. Heme can be formed from the hemoglobin in red blood cells. The iron from the heme group is recycled back to the bone marrow when the heme is converted into biliverdin. Notice that carbon monoxide is produced in this process and because it is toxic, must be eliminated from the body.

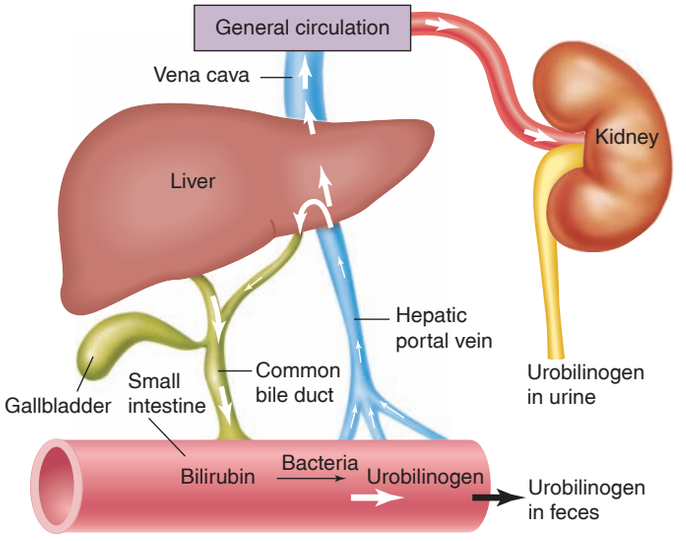

Figure 18.23 The enterohepatic circulation of urobilinogen. Bacteria in the intestine convert bilirubin (bile pigment) into urobilinogen. Some of this pigment leaves the body in the feces; some is absorbed by the intestine and is recycled through the liver. A portion of the urobilinogen that is absorbed enters the general circulation and is filtered by the kidneys into the urine.

Bile pigment, or **bilirubin,** is produced in the spleen, liver, and bone marrow as a derivative of the heme groups (minus the iron) from hemoglobin (fig. 18.22). The **free bilirubin** is not very water-soluble, and thus most is carried in the blood attached to albumin proteins. This protein-bound bilirubin can neither be filtered by the kidneys into the urine nor directly excreted by the liver into the bile.

The liver can take some of the free bilirubin out of the blood and conjugate (combine) it with glucuronic acid. This **conjugated bilirubin** is water-soluble and can be secreted into the bile. Once in the bile, the conjugated bilirubin can enter the intestine where it is converted by bacteria into another pigment—**urobilinogen.** Derivatives of urobilinogen impart a brown color to the feces. About 30% to 50% of the urobilinogen, however, is absorbed by the intestine and enters the hepatic portal vein. Of the urobilinogen that enters the liver sinusoids, some is secreted into the bile and is thus returned to the intestine in an enterohepatic circulation; the rest enters the general circulation (fig. 18.23). The urobilinogen in plasma, unlike free bilirubin, is not attached to albumin. Urobilinogen is therefore easily filtered by the kidneys into the urine where its derivatives produce an amber color.

Bile acids are derivatives of cholesterol that have two to four polar groups on each molecule. The principal bile acids in humans are *cholic acid* (fig. 18.24) and *chenodeoxycholic acid,* conjugated with the amino acids glycine or taurine to form the **bile salts.** In aqueous solutions these molecules "huddle" together to form aggregates known as **micelles** (fig. 18.24). The nonpolar parts are located in the central region of the micelle (away from water), whereas the polar groups face water around the periphery of the micelle (chapter 2; see fig. 2.22). Lecithin, cholesterol, and other lipids in the small intestine enter these micelles, and the dual nature of the bile salts (part polar, part nonpolar) allows them to emulsify fat in the chyme.

The liver's production of bile acids from cholesterol is the major pathway of cholesterol breakdown in the body. This amounts to about half a gram of cholesterol converted into bile acids per day. No more than this is required, because approximately 95% of the bile acids released into the duodenum are absorbed in the ileum by means of specific carriers, and so have an enterohepatic circulation. Bile salts recirculate 6 to 10 times per day, with only about 0.5 g excreted in the feces.

CLINICAL APPLICATION

Jaundice is a yellow staining of the tissues produced by high blood concentrations of either free or conjugated bilirubin. Jaundice associated with high blood levels of conjugated bilirubin in adults may occur when bile excretion is blocked by gallstones. Because free bilirubin is derived from heme, jaundice associated with high blood levels of free bilirubin is usually caused by an excessively high rate of red blood cell destruction. This is the cause of jaundice in infants who suffer from *hemolytic disease of the newborn,* or *erythroblastosis fetalis. Physiological jaundice of the newborn* is due to high levels of free bilirubin in otherwise healthy neonates. This type of jaundice may be caused by the rapid fall in blood hemoglobin concentrations that normally occurs at birth. In premature infants, it may be caused by inadequate amounts of hepatic enzymes that are needed to conjugate bilirubin so that it can be excreted in the bile.

Newborn infants with jaundice are usually treated by exposing them to blue light in the wavelength range of 400 to 500 nm. This light is absorbed by bilirubin in cutaneous vessels and results in the conversion of the bilirubin into a more polar form that can be dissolved in plasma without having to be conjugated with glucuronic acid. This more water-soluble photoisomer of bilirubin can then be excreted in the bile and urine.

Case Investigation CLUES

Alan had yellowing of his sclera, and his blood tests revealed elevated levels of conjugated bilirubin.

- What does the yellowing of the sclera indicate, and what is its cause?
- What could cause the elevation in conjugated bilirubin?

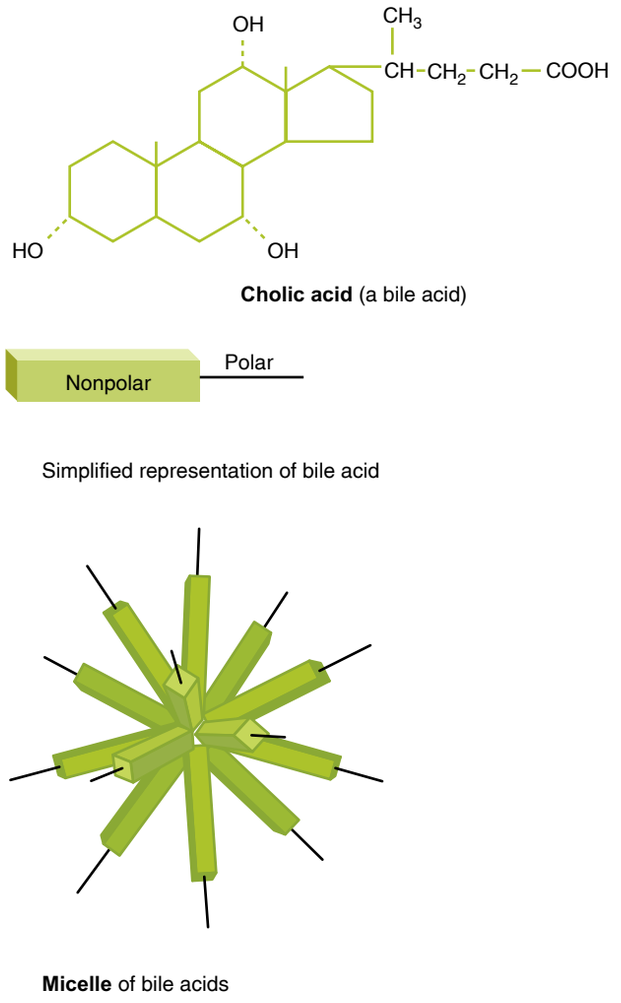

Figure 18.24 **Bile acids form micelles.** (*a*) Cholic acid, a bile acid. (*b*) A simplified representation of a bile acid, emphasizing that part of the molecule is polar, but most is nonpolar. (*c*) Bile acids in water aggregate to form associations called micelles. Cholesterol and lecithin, being nonpolar, can enter the micelles. The bile acids in the micelles serve to emulsify triglycerides (fats and oils) in the chyme.

Detoxication of the Blood

The liver can remove hormones, drugs, and other biologically active molecules from the blood by (1) excretion of these compounds in the bile as previously described; (2) phagocytosis by the Kupffer cells that line the sinusoids; and (3) chemical alteration of these molecules within the hepatocytes.

Ammonia, for example, is a very toxic molecule produced by deamination of amino acids in the liver and by the action of bacteria in the intestine. Because the ammonia concentration of portal vein blood is 4 to 50 times greater than that of blood in the hepatic vein, it is clear that the ammonia is removed by the liver. The liver has the enzymes needed to convert ammonia into less toxic **urea** molecules (chapter 5; see fig. 5.16), which are secreted by the liver into the blood and excreted by the kidneys in the urine. Similarly, the liver converts toxic porphyrins into **bilirubin** and toxic purines into **uric acid.**

Steroid hormones and many drugs are inactivated in their passage through the liver by modifications of their chemical structures. The liver has enzymes that convert these nonpolar molecules into more polar (more water-soluble) forms by *hydroxylation* (the addition of OH^- groups) and by *conjugation* with highly polar groups such as sulfate and glucuronic acid. Polar derivatives of steroid hormones and drugs are less biologically active and, because of their increased water solubility, are more easily excreted by the kidneys into the urine.

Conjugation of steroid hormones and *xenobiotics* (foreign chemicals that are biologically active) makes them anionic (negatively charged) and hydrophilic (water-soluble). Thus changed, these compounds can be transported by liver cells into the bile canaliculi by **multispecific organic anion transport** carriers. These carriers have been cloned and identified as the same type that transports similar molecules into the nephron tubules. Through renal secretion (chapter 17) and secretion into the bile, therefore, these transport carriers help the body to eliminate potentially toxic molecules.

CLINICAL APPLICATION

The liver cells contain enzymes for the metabolism of steroid hormones and other endogenous molecules, as well as for the detoxication of such exogenous toxic compounds as benzopyrene (a carcinogen from tobacco smoke and charbroiled meat), polychlorinated biphenyls (PCBs), and dioxin. The enzymes are members of a class called the **cytochrome P450 enzymes** that comprises a few dozen enzymes with varying specificities. Together, these enzymes can metabolize thousands of toxic compounds. Because people vary in their hepatic content of the different cytochrome P450 enzymes, one person's sensitivity to a drug may be greater than another's because of a relative deficiency in the appropriate cytochrome P450 enzyme needed to metabolize that drug.

The cytochrome P450 enzymes in the liver contain heme groups, like the heme in hemoglobin. Heme is classified chemically as a *porphyrin,* and excessive amounts are toxic to the bone marrow or liver. This condition is called **porphyria.** Porphyria is caused by genetic mutations that damage one of several enzymes required for the synthesis of heme, resulting in the accumulation of porphyrin heme precursors. Hepatic porphyria can produce abdominal pain, as well as neurological and psychological disturbances. Indeed, there is evidence that porphyria may have caused the "madness" of King George III, and may also have afflicted Friedrich Wilhelm I of Prussia and the artist Vincent Van Gogh.

Production of the cytochrome P450 enzymes, needed for the hepatic metabolism of lipophilic compounds such as steroid hormones and drugs, is stimulated by the activation of a nuclear receptor. Nuclear receptors bind to particular molecular ligands and then activate specific genes (chapter 11; see fig. 11.5). The particular nuclear receptor that stimulates the production of cytochrome P450 enzymes is known as *SXR*—for *steroid and xenobiotic receptor.* A drug that activates SXR, and thereby induces the production of cytochrome P450 enzymes, would thus be expected to increase the hepatic metabolism of many other drugs. This is the mechanism responsible for many interactions among different drugs.

Secretion of Glucose, Triglycerides, and Ketone Bodies

The liver helps regulate the blood glucose concentration by either removing glucose from the blood or adding glucose to it, according to the needs of the body (chapter 5; see fig. 5.5). After a carbohydrate-rich meal, the liver can remove some glucose from the hepatic portal blood and convert it into glycogen and triglycerides through the processes of **glycogenesis** and **lipogenesis,** respectively. During fasting, the liver secretes glucose into the blood. This glucose can be derived from the breakdown of stored glycogen in a process called **glycogenolysis,** or it can be produced by the conversion of noncarbohydrate molecules (such as amino acids) into glucose in a process called **gluconeogenesis.** The liver also contains the enzymes required to convert free fatty acids into ketone bodies (**ketogenesis**), which are secreted into the blood in large amounts during fasting. These processes are controlled by hormones and are explained further in chapter 19 (see figs. 19.6 and 19.9).

Production of Plasma Proteins

Plasma albumin and most of the plasma globulins (with the exception of immunoglobulins, or antibodies) are produced by the liver. Albumin constitutes about 70% of the total plasma protein and contributes most to the colloid osmotic pressure of the blood (chapter 14, section 14.2). The globulins produced by the liver have a wide variety of functions, including transport of cholesterol and triglycerides, transport of steroid and thyroid hormones, inhibition of trypsin activity, and blood clotting. Clotting factors I (fibrinogen), II (prothrombin), III, V, VII, IX, and XI, as well as angiotensinogen, are all produced by the liver.

Gallbladder

The **gallbladder** is a saclike organ attached to the inferior surface of the liver. This organ stores and concentrates bile, which drains to it from the liver by way of the bile ducts, hepatic ducts, and *cystic duct,* respectively. A sphincter valve at the neck of the gallbladder allows a 35- to 100-ml storage capacity. When the gallbladder fills with bile, it expands to the size and shape of a small pear. Bile is a yellowish green fluid containing bile salts, bilirubin, cholesterol, and other compounds, as previously discussed. Contraction of the muscularis layer of the gallbladder ejects bile through the cystic duct into the *common bile duct,* which conveys bile into the duodenum (fig. 18.25).

Bile is continuously produced by the liver and drains through the hepatic and common bile ducts to the duodenum. When the small intestine is empty of food, the *sphincter of ampulla (sphincter of Oddi)* at the end of the common bile duct closes, and bile is forced up to the cystic duct and then to the gallbladder for storage.

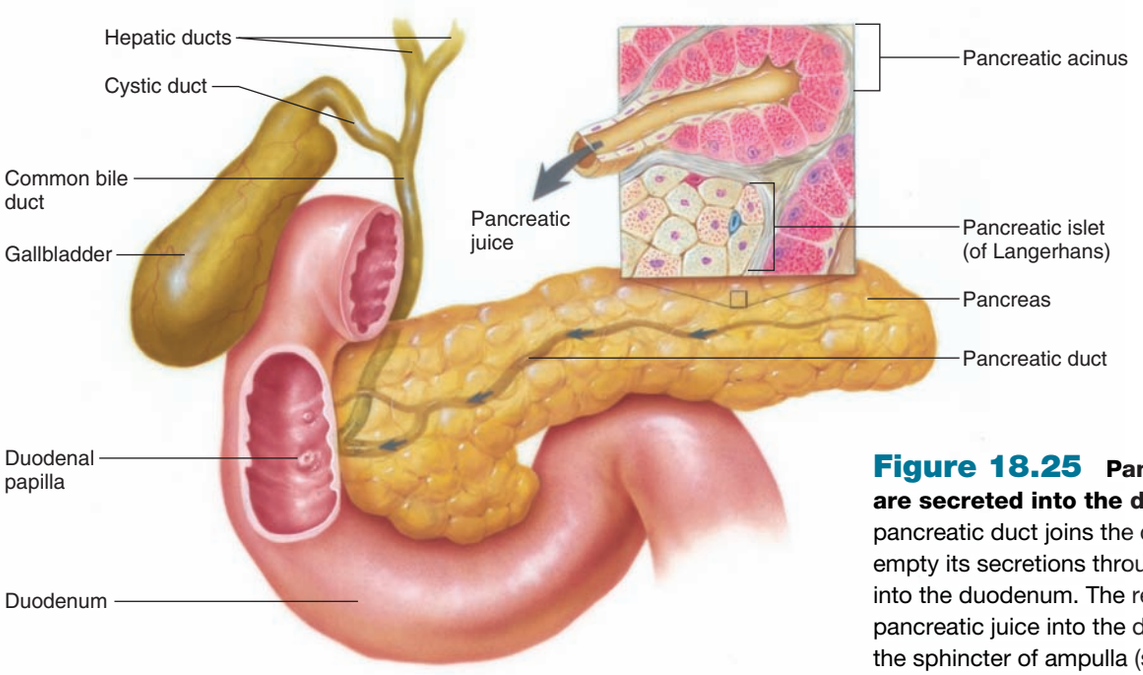

Figure 18.25 Pancreatic juice and bile are secreted into the duodenum. The pancreatic duct joins the common bile duct to empty its secretions through the duodenal papilla into the duodenum. The release of bile and pancreatic juice into the duodenum is controlled by the sphincter of ampulla (sphincter of Oddi).

CLINICAL APPLICATION

Approximately 20 million Americans have **gallstones**—small, hard mineral deposits (calculi) that can produce painful symptoms by obstructing the cystic or common bile ducts. Gallstones commonly contain cholesterol as their major component; indeed, cholesterol was discovered in 1789 when it was first isolated from gallstones. Cholesterol normally has an extremely low water solubility (20 μg/L), but it can be present in bile at 2 million times its water solubility (40 g/L) because cholesterol molecules cluster together with bile salts and lecithin in the hydrophobic centers of micelles. In order for gallstones to be produced, the liver must secrete enough cholesterol to create a supersaturated solution. The gallbladder then secretes excess mucus that serves as a nucleating agent for the formation of solid cholesterol crystals (fig. 18.26). The combination of these crystals and the mucus form a sludge that impedes the emptying of the gallbladder. In some cases, cholesterol gallstones may be dissolved by oral ingestion of bile acids. This may be combined with a treatment that involves fragmentation of the gallstones by high-energy shock waves delivered to a patient immersed in a water bath. The most common and effective treatment, however, is surgical removal of the gallbladder using a procedure called *laparoscopic cholecystectomy.*

Case Investigation CLUE

Alan had pain below his right scapula whenever he ate foods such as peanut butter or bacon, which are oily or fatty.

- If this pain was caused by a gallstone, how might that relate to Alan's high blood levels of conjugated bilirubin and jaundice?

Pancreas

The **pancreas** is a soft, glandular organ that has both exocrine and endocrine functions (fig. 18.27). The endocrine function is performed by clusters of cells called the **pancreatic islets,** or **islets of Langerhans** (fig. 18.27*a*), that secrete the hormones insulin and glucagon into the blood (chapter 19, section 19.3). As an exocrine gland, the pancreas secretes pancreatic juice through the pancreatic duct into the duodenum. Within the lobules of the pancreas are the exocrine secretory units, called **acini** (fig. 18.27*b*). Each acinus consists of a single layer of acinar epithelial cells surrounding a lumen, into which the constituents of pancreatic juice are secreted.

Pancreatic Juice

Pancreatic juice contains *bicarbonate* and about 20 different digestive enzymes. These enzymes include (1) **amylase,** which digests starch; (2) **trypsin,** which digests protein; and (3) **lipase,** which digests triglycerides. Other pancreatic enzymes are listed in table 18.4. It should be noted that the complete digestion of food molecules in the small intestine requires the action of both pancreatic enzymes and brush border enzymes.

Evidence suggests that bicarbonate is secreted into the pancreatic juice by the cells that line the ductules, rather than by the acinar cells (see fig. 18.27*b*). The bicarbonate is produced from CO_2 that diffuses into the cells from the blood. This occurs

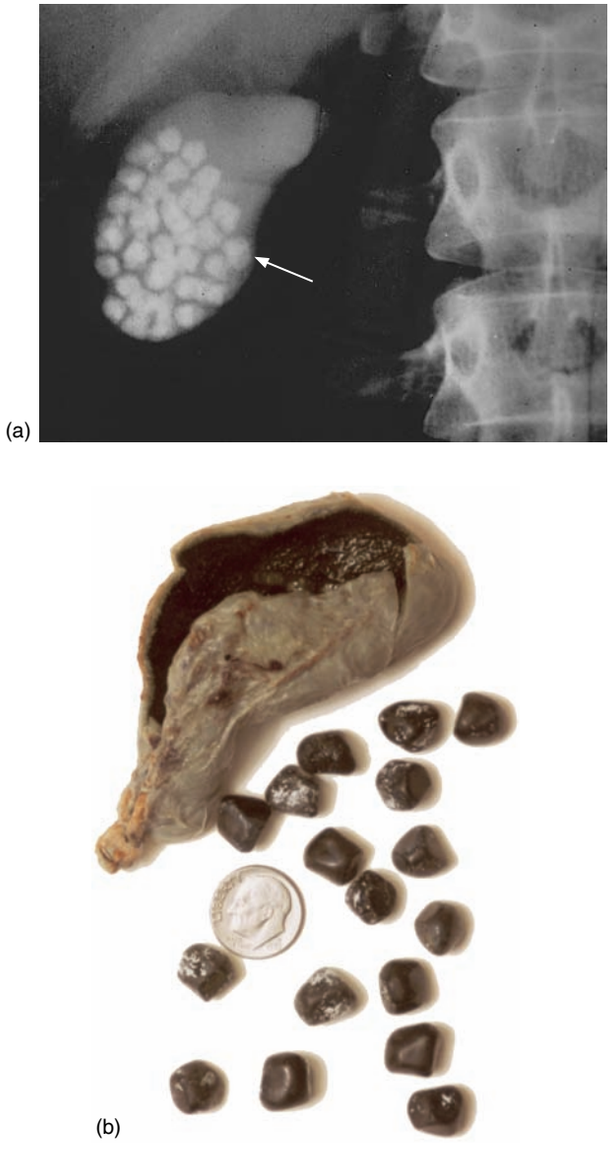

Figure 18.26 **Gallstones.** (*a*) A radiograph of a gallbladder that contains gallstones (biliary calculi). (*b*) A posterior view of a gallbladder that has been surgically removed (cholecystectomy) and cut open to reveal its gallstones. (Note their size relative to that of a dime.)

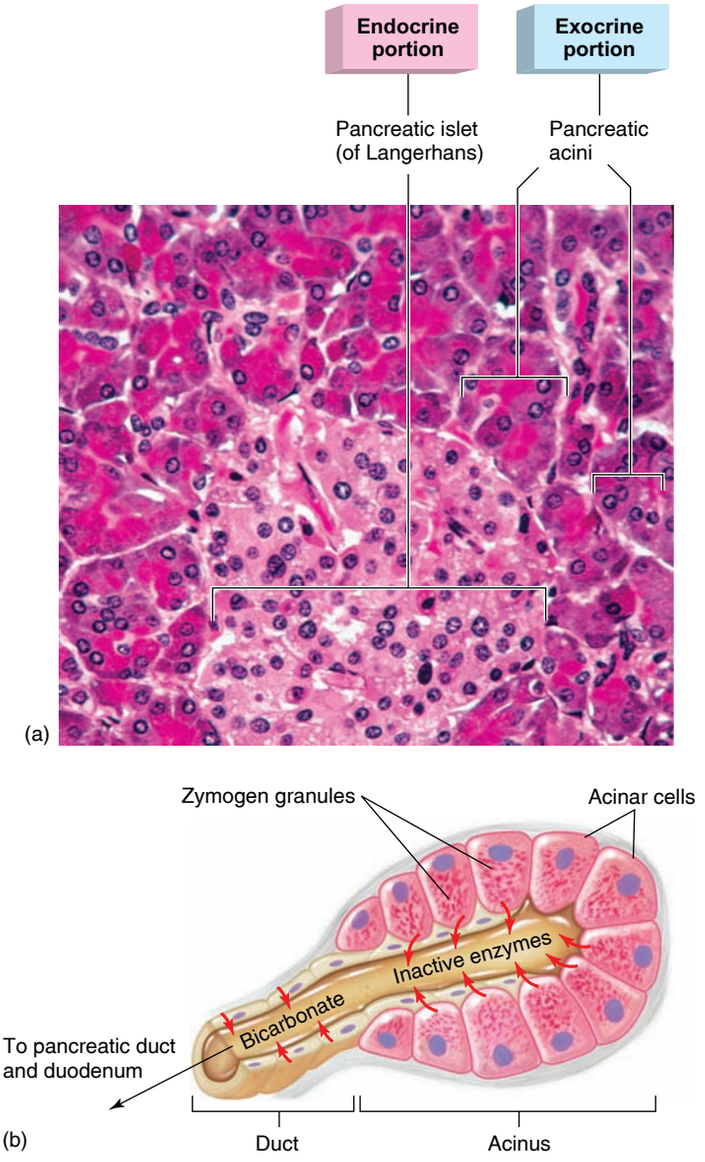

Figure 18.27 **The pancreas is both an exocrine and an endocrine gland.** (*a*) A photomicrograph of the endocrine and exocrine portions of the pancreas. (*b*) An illustration depicting the exocrine pancreatic acini, where the acinar cells produce inactive enzymes stored in zymogen granules. The inactive enzymes are secreted by way of a duct system into the duodenum.

because of the formation of carbonic acid (from CO_2 and H_2O, in a reaction catalyzed by carbonic anhydrase), which dissociates to form bicarbonate (HCO_3^-) and H^+. The H^+ is secreted into the blood and the HCO_3^- is secreted into the pancreatic juice (fig. 18.28). This is similar to the process of acid secretion by parietal cells of the stomach, but with a reversed direction.

Secretion of HCO_3^- from the ductule cells into the lumen is accompanied by movement of Cl^- in the opposite direction. Interestingly, the *cystic fibrosis transmembrane conductance regulator (CFTR),* a channel for the facilitated diffusion of Cl^-, is located in the ductule cells on the membrane facing the lumen. Here, the CFTR promotes diffusion of Cl^- out of the ductule cells and back into the lumen (fig. 18.28). This is medically important because people with cystic fibrosis (who have defective CFTR function) have a greatly diminished ability to secrete HCO_3^- into the pancreatic juice. This is believed to cause digestive enzymes to build up in the pancreas and become prematurely activated, eventually leading to destruction of the pancreas.

Most pancreatic enzymes are produced as inactive molecules, or *zymogens,* so that the risk of self-digestion within

Table 18.4 | Enzymes Contained in Pancreatic Juice

Enzyme	Zymogen	Activator	Action
Trypsin	Trypsinogen	Enterokinase	Cleaves internal peptide bonds
Chymotrypsin	Chymotrypsinogen	Trypsin	Cleaves internal peptide bonds
Elastase	Proelastase	Trypsin	Cleaves internal peptide bonds
Carboxypeptidase	Procarboxypeptidase	Trypsin	Cleaves last amino acid from carboxyl-terminal end of polypeptide
Phospholipase	Prophospholipase	Trypsin	Cleaves fatty acids from phospholipids such as lecithin
Lipase	None	None	Cleaves fatty acids from glycerol
Amylase	None	None	Digests starch to maltose and short chains of glucose molecules
Cholesterolesterase	None	None	Releases cholesterol from its bonds with other molecules
Ribonuclease	None	None	Cleaves RNA to form short chains
Deoxyribonuclease	None	None	Cleaves DNA to form short chains

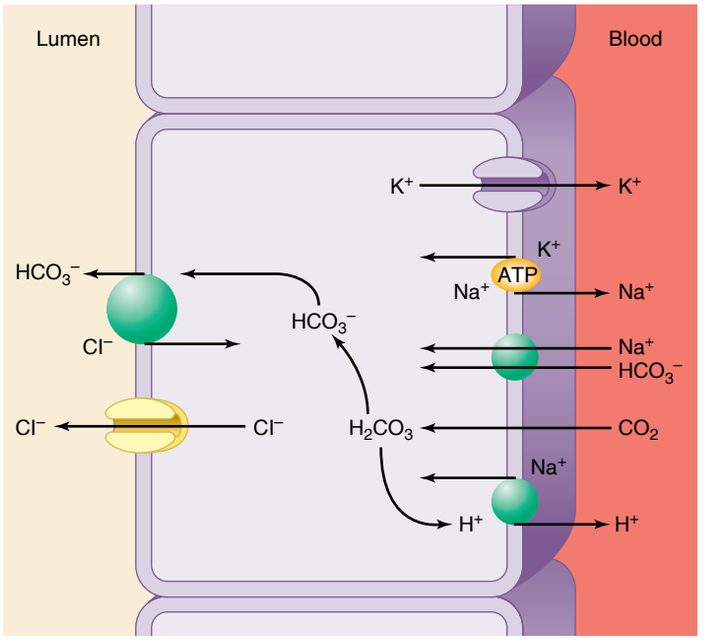

Figure 18.28 Secretion of bicarbonate into pancreatic juice. Cells of the pancreatic duct take in CO_2 from the blood and use it to generate carbonic acid (H_2CO_3). This dissociates into bicarbonate (HCO_3^-) and H^+. The HCO_3^- is secreted into the lumen of the duct by a carrier that exchanges it for Cl^-. The Cl^- then leaks passively back into the lumen through a different, CFTR chloride channel (see text for details).

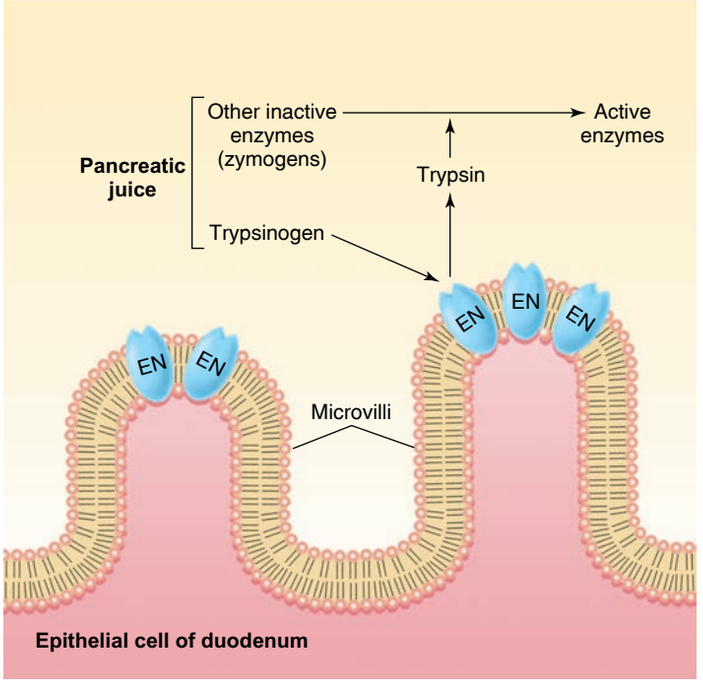

Figure 18.29 The activation of pancreatic juice enzymes. The pancreatic protein-digesting enzyme trypsin is secreted in an inactive form known as trypsinogen. This inactive enzyme (zymogen) is activated by a brush border enzyme, enterokinase (EN), located in the cell membrane of microvilli. Active trypsin in turn activates other zymogens in pancreatic juice.

the pancreas is minimized. The inactive form of trypsin, called trypsinogen, is activated within the small intestine by the catalytic action of the brush border enzyme *enterokinase.* Enterokinase converts trypsinogen to active trypsin. Trypsin, in turn, activates the other zymogens of pancreatic juice (fig. 18.29) by cleaving off polypeptide sequences that inhibit the activity of these enzymes.

The activation of trypsin, therefore, is the triggering event for the activation of other pancreatic enzymes. Actually, the pancreas does produce small amounts of active trypsin, but the other enzymes are not activated until pancreatic juice has entered the duodenum. This is because pancreatic juice also contains a small protein called *pancreatic trypsin inhibitor* that attaches to trypsin and inhibits its activity in the pancreas.

CLINICAL APPLICATION

Pancreatitis (inflammation of the pancreas) may result when conditions such as alcoholism, gallstones, traumatic injury, infections, or toxicosis from various drugs provoke activation of digestive enzymes within the pancreas. Leakage of trypsin into the blood also occurs, but trypsin is inactive in the blood because of the inhibitory action of two plasma proteins, α_1-antitrypsin and α_2-macroglobulin. Pancreatic amylase may also leak into the blood, but it is not active because its substrate (starch) is not present in blood. Pancreatic amylase activity can be measured *in vitro,* however, and these measurements are commonly performed to assess the health of the pancreas.

CHECKPOINT

15. Describe the structure of liver lobules, and trace the pathways for the flow of blood and bile in the lobules.
16. Describe the composition and function of bile, and trace the flow of bile from the liver and gallbladder to the duodenum.
17. Explain how the liver inactivates and excretes compounds such as hormones and drugs.
18. Describe the enterohepatic circulation of bilirubin and urobilinogen.
19. Explain how the liver helps maintain a constant blood glucose concentration and how the pattern of venous blood flow permits this function.
20. Describe the endocrine and exocrine structures and functions of the pancreas. How is the pancreas protected against self-digestion?

18.6 NEURAL AND ENDOCRINE REGULATION OF THE DIGESTIVE SYSTEM

The stomach begins to increase its secretion in anticipation of a meal, and further increases its activities in response to the arrival of food. The entry of chyme into the duodenum stimulates the secretion of hormones that promote contractions of the gallbladder, the secretion of pancreatic juice, and the inhibition of gastric activity.

LEARNING OUTCOMES

After studying this section, you should be able to:

- Identify the phases and explain the mechanisms of gastric regulation
- Explain the regulation of pancreatic juice and bile secretion
- Explain the significance of the enteric nervous system

Neural and endocrine control mechanisms modify the activity of the digestive system. The sight, smell, or taste of food, for example, can stimulate salivary and gastric secretions via activation of the vagus nerves, which help "prime" the digestive system in preparation for a meal. Stimulation of the vagus, in this case, originates in the brain and is a conditioned reflex (as Pavlov demonstrated by training dogs to salivate in response to a bell). The vagus nerves are also involved in the reflex control of one part of the digestive system by another—these are "short reflexes," which do not involve the brain.

The GI tract is both an endocrine gland and a target for the action of various hormones. Indeed, the first hormones to be discovered were gastrointestinal hormones. In 1902 two English physiologists, Sir William Bayliss and Ernest Starling, discovered that the duodenum produced a chemical regulator. They named this substance **secretin,** and proposed in 1905 that it was but one of many yet undiscovered chemical regulators produced by the body. Bayliss and Starling coined the term *hormones* for this new class of regulators. In that same year other investigators discovered that an extract from the stomach antrum stimulated gastric secretion. The hormone **gastrin** was thus the second hormone to be discovered.

The chemical structures of gastrin, secretin, and the duodenal hormone **cholecystokinin (CCK)** were determined in the 1960s. More recently, a fourth hormone produced by the small intestine, **gastric inhibitory peptide (GIP),** has been added to the list of proven GI tract hormones. The effects of these and other gastrointestinal hormones are summarized in table 18.5.

Regulation of Gastric Function

Gastric motility and secretion are to some extent automatic. Waves of contraction that serve to push chyme through the pyloric sphincter, for example, are initiated spontaneously by pacesetter cells in the greater curvature of the stomach. Likewise, the secretion of HCl from parietal cells and pepsinogen from chief cells can be stimulated in the absence of neural and hormonal influences by the presence of cooked or partially digested protein in the stomach. This action involves other cells in the gastric mucosa, including the G cells, which secrete the hormone gastrin; the enterochromaffin-like (ECL) cells, which secrete histamine; and the D cells, which secrete somatostatin.

Table 18.5 | Effects of Gastrointestinal Hormones

Secreted by	Hormone	Effects
Stomach	Gastrin	Stimulates parietal cells to secrete HCl Stimulates chief cells to secrete pepsinogen Maintains structure of gastric mucosa
Small intestine	Secretin	Stimulates water and bicarbonate secretion in pancreatic juice Potentiates actions of cholecystokinin on pancreas
Small intestine	Cholecystokinin (CCK)	Stimulates contraction of gallbladder Stimulates secretion of pancreatic juice enzymes Inhibits gastric motility and secretion Maintains structure of exocrine pancreas (acini)
Small intestine	Gastric inhibitory peptide (GIP)	Inhibits gastric motility and secretion Stimulates secretion of insulin from pancreatic islets
Ileum and colon	Glucagon-like peptide-I (GLP-I)	Inhibits gastric motility and secretion Stimulates secretion of insulin from pancreatic islets
	Guanylin	Stimulates intestinal secretion of Cl^-, causing elimination of NaCl and water in the feces

The effects of autonomic nerves and hormones are superimposed on this automatic activity. This extrinsic control of gastric function is conveniently divided into three phases: (1) the *cephalic phase;* (2) the *gastric phase;* and (3) the *intestinal phase.* These are summarized in table 18.6.

Cephalic Phase

The **cephalic phase** of gastric regulation refers to control by the brain via the vagus nerves. As previously discussed, various conditioned stimuli can evoke gastric secretion. This conditioning in humans is, of course, more subtle than that exhibited by Pavlov's dogs in response to a bell. In fact, just talking about appetizing food is sometimes a more potent stimulus for gastric acid secretion than the actual sight and smell of food.

Activation of the vagus nerves stimulates the chief cells to secrete pepsinogen. Neurotransmitters released by the vagus also stimulate the secretion of HCl by the parietal cells. This neural stimulation of HCl secretion may be partly direct, through ACh binding to muscarinic receptors on the parietal cell membrane. However, the major mechanism of neural stimulation is indirect, through the stimulation of histamine secretion by ECL cells. The histamine secreted by the ECL cells then stimulates the parietal cells to secrete HCl (fig. 18.30).

This cephalic phase continues into the first 30 minutes of a meal, but then gradually declines in importance as the next phase becomes predominant.

Gastric Phase

The arrival of food into the stomach stimulates the **gastric phase** of regulation. Gastric secretion is stimulated in response to two factors: (1) distension of the stomach, which

Table 18.6 | The Three Phases of Gastric Secretion

Phase of Regulation	Description
Cephalic Phase	1. Sight, smell, and taste of food cause stimulation of vagus nuclei in brain 2. Vagus stimulates acid secretion a. Indirect stimulation of parietal cells (major effect) b. Stimulation of gastrin secretion (lesser effect)
Gastric Phase	1. Distension of stomach stimulates vagus nerve; vagus stimulates acid secretion 2. Amino acids and peptides in stomach lumen stimulate acid secretion a. Direct stimulation of parietal cells (lesser effect) b. Stimulation of gastrin secretion; gastrin stimulates acid secretion (major effect) 3. Gastrin secretion inhibited when pH of gastric juice falls below 2.5
Intestinal Phase	1. Neural inhibition of gastric emptying and acid secretion a. Arrival of chyme in duodenum causes distension, increase in osmotic pressure b. These stimuli activate a neural reflex that inhibits gastric activity 2. In response to fat in chyme, duodenum secretes a hormone that inhibits gastric acid secretion

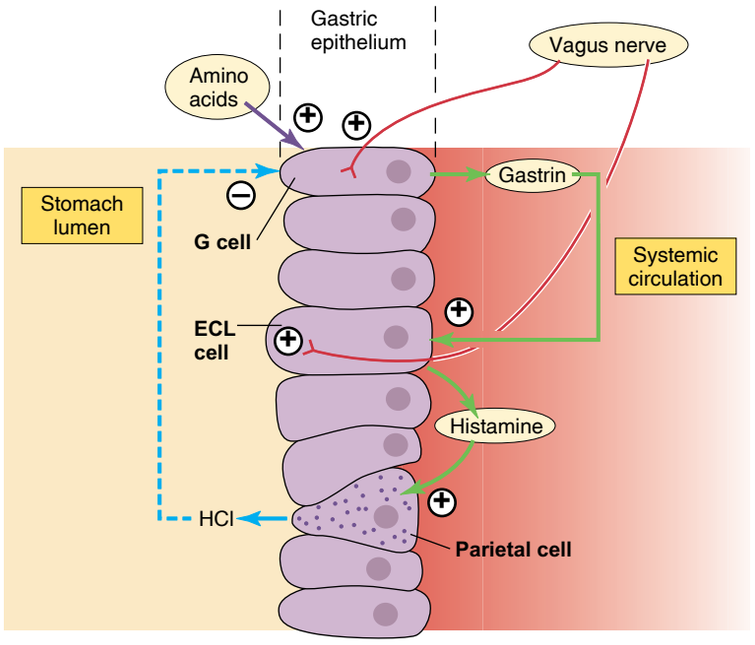

Figure 18.30 The regulation of gastric acid secretion. The presence of amino acids in the stomach lumen from partially digested proteins stimulates gastrin secretion. Gastrin secretion from G cells is also stimulated by vagus nerve activity. The secreted gastrin then acts as a hormone to stimulate histamine release from the ECL cells. The histamine, in turn, acts as a paracrine regulator to stimulate the parietal cells to secrete HCl. (⊕ = stimulation; ⊖ = inhibition.)

is determined by the amount of chyme, and (2) the chemical nature of the chyme.

Although intact proteins in the chyme have little stimulatory effect, the partial digestion of proteins into shorter polypeptides and amino acids, particularly phenylalanine and tryptophan, stimulates the chief cells to secrete pepsinogen and the G cells to secrete gastrin. Gastrin, in turn, stimulates the secretion of pepsinogen from chief cells and HCl from parietal cells, but its effect on the parietal cells is primarily indirect. Gastrin stimulates the secretion of histamine from ECL cells, and the histamine then stimulates secretion of HCl from parietal cells (fig. 18.30). A *positive feedback mechanism* thus develops. As more HCl and pepsinogen are secreted, more short polypeptides and amino acids are released from the ingested proteins. This stimulates additional secretion of gastrin and, therefore, additional secretion of HCl and pepsinogen. It should be noted that glucose in the chyme has no effect on gastric secretion, and the presence of fat inhibits acid secretion.

Secretion of HCl during the gastric phase is also regulated by a *negative feedback mechanism.* As the pH of gastric juice drops, so does the secretion of gastrin—at a pH of 2.5, gastrin secretion is reduced, and at a pH of 1.0 gastrin secretion ceases. The secretion of HCl thus declines accordingly. This effect may be mediated by the hormone somatostatin, secreted by the D cells of the gastric mucosa. As the pH of gastric juice falls, the D cells are stimulated to secrete somatostatin, which then acts as a paracrine regulator to inhibit the secretion of gastrin from the G cells.

The presence of proteins and polypeptides in the stomach helps buffer the acid and thus helps prevent a rapid fall in gastric pH. More acid can thus be secreted when proteins are present than when they are absent. In summary, arrival of protein into the stomach stimulates acid secretion in two ways—by the positive feedback mechanism previously discussed and by inhibition of the negative feedback control of acid secretion. Through these mechanisms, the amount of acid secreted is closely matched to the amount of protein ingested. As the stomach is emptied and the protein buffers exit, the pH falls, and the secretion of gastrin and HCl is accordingly inhibited.

Intestinal Phase

The **intestinal phase** of gastric regulation refers to the inhibition of gastric activity when chyme enters the small intestine. Investigators in 1886 demonstrated that the addition of olive oil to a meal inhibits gastric emptying, and in 1929 it was shown that the presence of fat inhibits gastric juice secretion. This inhibitory intestinal phase of gastric regulation is due to both a neural reflex originating from the duodenum and a chemical hormone secreted by the duodenum.

The arrival of chyme into the duodenum increases its osmolality. This stimulus, together with stretch of the duodenum and possibly other stimuli, activates sensory neurons of the vagus nerves and produces a neural reflex that inhibits gastric motility and secretion. The presence of fat in the chyme also stimulates the duodenum to secrete a hormone that inhibits gastric function. The general term for such an inhibitory hormone is an **enterogastrone.**

Several hormones secreted by the small intestine have been shown to have an enterogastrone effect. One of these hormones was even named for this action—*gastric inhibitory peptide (GIP),* secreted by the duodenum. However, subsequent research demonstrated that the major action of GIP is actually to stimulate insulin secretion (from the beta cells of the pancreatic islets) in response to glucose in food. As a consequence of this action, the acronym of the hormone was retained but it was renamed **glucose-dependent insulinotropic peptide (GIP).**

Other polypeptide hormones secreted by the small intestine that have an enterogastrone effect include **somatostatin,** produced by the stomach and intestine (as well as the brain); **cholecystokinin (CCK),** secreted by the duodenum in response to the presence of chyme; and **glucagon-like peptide-1 (GLP-1),** secreted by the ileum. These hormones help reduce gastric activity once the small intestine has received a load of chyme from the stomach, giving the intestine time to digest and absorb the food.

Interestingly, GLP-1, like GIP, is a very powerful stimulator of insulin secretion from the pancreatic islets. These two intestinal hormones stimulate the pancreatic islets to "anticipate" a rise in blood glucose by starting to secrete insulin

even before the orally ingested glucose has been absorbed into the blood. Since insulin acts to lower the blood glucose concentration, this action helps maintain homeostasis of blood glucose (chapter 19, section 19.3).

FITNESS APPLICATION

The inhibitory neural and endocrine mechanisms during the intestinal phase prevent the further passage of chyme from the stomach to the duodenum. This gives the duodenum time to process the load of chyme received previously. Since secretion of the enterogastrone is stimulated by fat in the chyme, a breakfast of bacon and eggs takes longer to pass through the stomach—and makes one feel "fuller" for a longer time—than does a breakfast of pancakes and syrup.

Regulation of Intestinal Function

Enteric Nervous System

The neurons and glial cells of the **enteric nervous system (ENS)** are organized into ganglia that are interconnected by two plexuses. The outer *myenteric (Auerbach's) plexus* is found along the entire length of the GI tract; the inner *submucosal (Meissner's) plexus* is located only in the small and large intestine. The ENS contains about 100 million neurons (roughly the same number as in the spinal cord), and has a similar diversity of neurotransmitters as the CNS. The ENS has interneurons as well as sensory and autonomic motor neurons, and its glial cells resemble the astrocytes of the brain.

Some sensory (afferent) neurons within the intestinal plexuses travel in the vagus nerves to deliver sensory information to the CNS. These are called *extrinsic afferents,* and they are involved in regulation by the autonomic nervous system. Other sensory neurons—called *intrinsic afferents*—have their cell bodies in the myenteric or submucosal plexuses and synapse with the interneurons of the enteric nervous system.

Peristalsis, for example, is regulated by the enteric nervous system. A bolus of chyme stimulates intrinsic afferents (with cell bodies in the myenteric plexus) that activate enteric interneurons, which in turn stimulate motor neurons. These motor neurons innervate both smooth muscle cells and interstitial cells of Cajal, where they release excitatory and inhibitory neurotransmitters. Smooth muscle contraction is stimulated by the neurotransmitters ACh and substance P above the bolus, and smooth muscle relaxation is promoted by nitric oxide, vasoactive intestinal peptide (VIP), and ATP below the bolus (fig. 18.31).

Paracrine Regulators of the Intestine

There is evidence that the enterochromaffin-like cells (ECL cells) of the intestinal mucosa secrete **serotonin,** or **5-hydroxytryptamine,** in response to the stimuli of pressure and various chemicals. Serotonin then stimulates intrinsic afferents, which conduct impulses into the submucosal and myenteric plexuses and there activate motor neurons. Motor neurons that terminate in the muscularis can stimulate contractions; those that terminate in the intestinal crypts can stimulate the secretion of salt and water into the lumen. The ECL cells have also been shown to produce another paracrine regulator, termed **motilin,** which stimulates contraction in the duodenum and stomach antrum.

Guanylin is a recently discovered paracrine regulator produced by the ileum and colon. It derives its name from its ability to activate the enzyme guanylate cyclase, and thus to cause the production of cyclic GMP (cGMP) within the cytoplasm of intestinal epithelial cells. Acting through cGMP as a second messenger, guanylin stimulates the intestinal epithelial cells to secrete Cl^- and water and inhibits their absorption of Na^+. These actions increase the amount of salt and water lost from the body in the feces. A related polypeptide, called **uroguanylin,** has been found in the urine. This polypeptide appears to be produced by the intestine, and may therefore function as a hormone that stimulates the kidneys to excrete salt in the urine.

CLINICAL APPLICATION

Certain *Escherichia coli* bacteria produce *heat-stable enterotoxins* that are responsible for **traveler's diarrhea.** The enterotoxins act by stimulating the same receptors on the apical membranes of the intestinal epithelial cells that are activated by guanylin. By mimicking the actions of guanylin, the enterotoxins stimulate intestinal Cl^- and water secretion to produce diarrhea.

Intestinal Reflexes

There are several intestinal reflexes that are controlled locally, by means of the enteric nervous system and paracrine regulators, and extrinsically through the actions of the nerves and hormones previously discussed. These reflexes include:

1. the **gastroileal reflex,** in which increased gastric activity causes increased motility of the ileum and increased movements of chyme through the ileocecal sphincter;
2. the **ileogastric reflex,** in which distension of the ileum causes a decrease in gastric motility;
3. the **intestino-intestinal reflexes,** in which overdistension of one intestinal segment causes relaxation throughout the rest of the intestine.

Regulation of Pancreatic Juice and Bile Secretion

The arrival of chyme into the duodenum stimulates the intestinal phase of gastric regulation and, at the same time, stimulates reflex secretion of pancreatic juice and bile. The

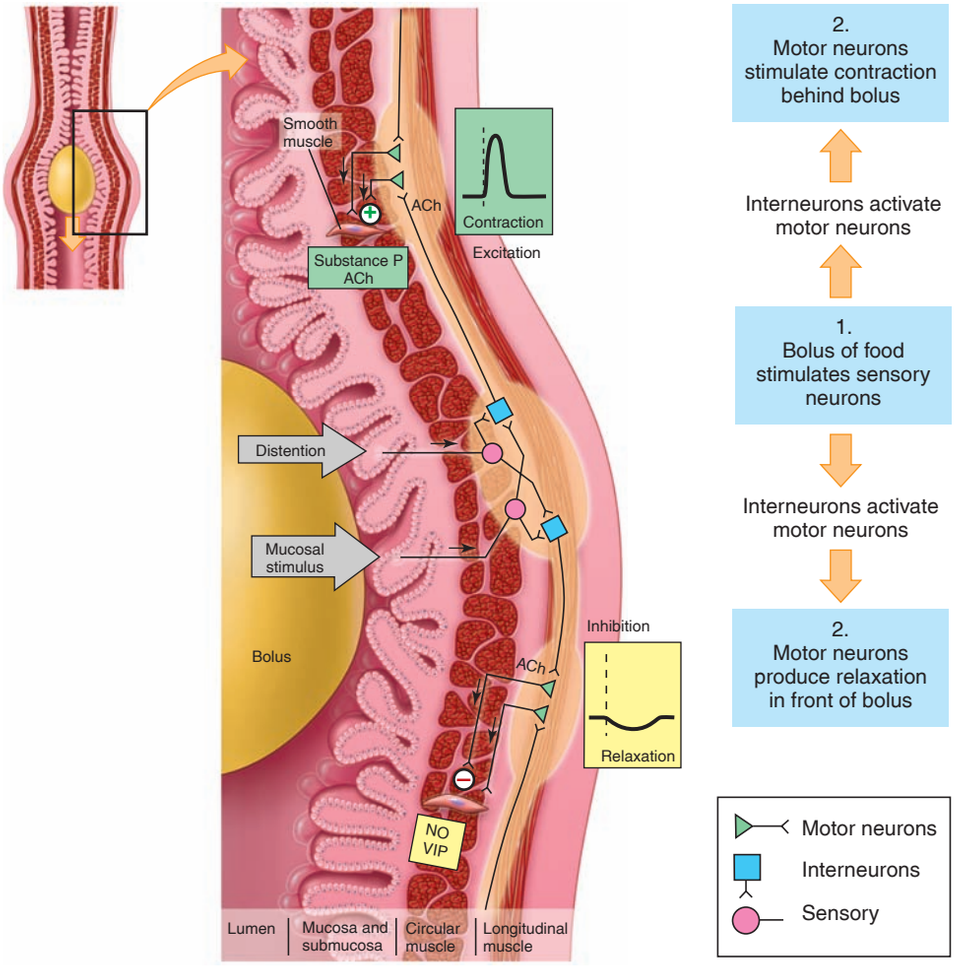

Figure 18.31 **The enteric nervous system coordinates peristalsis.** Peristalsis is produced by local reflexes involving the enteric nervous system. Notice that the enteric nervous system consists of motor neurons, interneurons, and sensory neurons. The neurotransmitters that stimulate smooth muscle contraction are indicated with a ⊕, while those that produce smooth muscle relaxation are indicated with a ⊖. (NO = nitric oxide; VIP = vasoactive intestinal peptide.)

entry of new chyme is thus retarded as the previous load is digested. The secretion of pancreatic juice and bile is stimulated both by neural reflexes initiated in the duodenum and by secretion of the duodenal hormones cholecystokinin and secretin.

Secretion of Pancreatic Juice

The secretion of pancreatic enzymes (including trypsin, lipase, and amylase) from the acinar cells is stimulated by ACh released by the vagus nerves, and by the hormone CCK secreted by the duodenum. Both ACh and CCK stimulate the acinar cells using a rise in cytoplasmic Ca^{2+} as a second messenger. Secretin, another hormone from the duodenum, can potentiate the effects of ACh and CCK on the acinar cells through the action of cyclic AMP as a second messenger.

The duodenum secretes CCK in response to the protein and fat content of the chyme, and the pancreatic juice enzymes released in response to CCK help digest these molecules. Partially digested protein and fat are the most potent stimulators of CCK secretion, and CCK secretion continues until the chyme has passed through the duodenum and early region of the jejunum.

By contrast, the duodenum releases the hormone secretin in response to a fall in the duodenal pH below 4.5. This low pH is maintained for only a short time, however, because secretin then stimulates the production of bicarbonate and its secretion into pancreatic juice. Because bicarbonate in pancreatic juice neutralizes the acidic chyme in the duodenum, the low pH of the chyme is soon raised by the alkaline pancreatic juice. This helps to protect the mucosa of the duodenum, and provides the pH environment for optimum activity of the pancreatic juice digestive enzymes.

Secretion of Bile

The liver secretes bile continuously, but bile secretion is increased by a meal. When bile arrives in the duodenum during a meal, the liver is stimulated to secrete more bile by the bile acids that return to the liver from the intestine via the hepatic portal vein (the enterohepatic circulation; see fig. 18.21). Endocrine and neural reflexes are also involved. Secretin stimulates the bile duct cells of the liver to secrete bicarbonate into the bile (leading to increased bile volume), and CCK enhances this effect. The secretion of CCK in response to fat in the chyme stimulates contractions of the gallbladder, allowing more bile to enter the duodenum. The bile then emulsifies the fat, aiding its digestion. Also, the arrival of chyme in the duodenum produces a neural reflex that stimulates contractions of the gallbladder.

Case Investigation CLUES

Alan's pain below his right scapula was triggered by eating peanut butter or bacon, but not by eating foods such as skinned chicken or fish.

- What component of the food was responsible for the painful reaction?
- How does this component of the food result in Alan's pain?

Trophic Effects of Gastrointestinal Hormones

Patients with tumors of the stomach pylorus exhibit excessive acid secretion and hyperplasia (growth) of the gastric mucosa. Surgical removal of the pylorus reduces gastric secretion and prevents growth of the gastric mucosa. Patients with peptic ulcers are sometimes treated by vagotomy—cutting of the portion of the vagus nerve that innervates the stomach. Vagotomy also reduces acid secretion but has no effect on the gastric mucosa. These observations suggest that the hormone gastrin, secreted by the pyloric mucosa, may exert stimulatory, or *trophic,* effects on the gastric mucosa. The structure of the gastric mucosa, in other words, is dependent upon the effects of gastrin.

In the same way, the structure of the acinar (exocrine) cells of the pancreas is dependent upon the trophic effects of CCK. Perhaps this explains why the pancreas, as well as the GI tract, atrophies during starvation. Since neural reflexes appear to be capable of regulating digestion, perhaps the primary function of the GI hormones is trophic—that is, maintenance of the structure of their target organs.

✔ CHECKPOINT

21. Describe the positive and negative feedback mechanisms that operate during the gastric phase of HCl and pepsinogen secretion.
22. Describe the mechanisms involved in the intestinal phase of gastric regulation, and explain why a fatty meal takes longer to leave the stomach than a meal low in fat.
23. Explain the hormonal mechanisms involved in the production and release of pancreatic juice and bile.
24. Describe the enteric nervous system, and identify some of the short reflexes that regulate intestinal function.

18.7 DIGESTION AND ABSORPTION OF CARBOHYDRATES, LIPIDS, AND PROTEINS

Polysaccharides and polypeptides are hydrolyzed into their subunits, which are secreted into blood capillaries. Fat is emulsified by bile salts, hydrolyzed into fatty acids and monoglycerides, and absorbed into the intestinal epithelial cells. Once inside the cells, triglycerides are resynthesized, combined with proteins, and secreted into the lymphatic fluid.

LEARNING OUTCOMES

After studying this section, you should be able to:

- ✔ Describe the processes involved in the digestion and absorption of carbohydrates and proteins
- ✔ Describe the processes involved in the digestion, absorption, and transport of dietary lipids

The caloric (energy) value of food is derived mainly from its content of carbohydrates, lipids, and proteins. In the average American diet, carbohydrates account for approximately 50% of the total calories, protein accounts for 11% to 14%, and lipids make up the balance. These food molecules consist primarily of long combinations of subunits (monomers) that must be digested by hydrolysis reactions into free monomers before absorption can occur. The characteristics of the major digestive enzymes are summarized in table 18.7.