21 The Digestive System

Give me a good digestion, Lord, and also something to digest.

Anonymous, *A Pilgrim's Grace*

BACKGROUND BASICS

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Cross-section of intestinal villa (outlined in red)

A shotgun wound to the stomach seems an unlikely beginning to the scientific study of digestive processes. But in 1822, at Fort Mackinac, a young Canadian trapper named Alexis St. Martin narrowly escaped death when a gun discharged three feet from him, tearing open his chest and abdomen and leaving a hole in his stomach wall. U.S. Army surgeon William Beaumont attended to St. Martin and nursed him back to health over the next two years.

The gaping wound over the stomach failed to heal properly, leaving a *fistula,* or opening, into the lumen. St. Martin was destitute and unable to care for himself, so Beaumont "retained St. Martin in his family for the special purpose of making physiological experiments." In a legal document, St. Martin even agreed to "obey, suffer, and comply with all reasonable and proper experiments of the said William [Beaumont] in relation to . . . the exhibiting . . . of his said stomach and the power and properties . . . and states of the contents thereof."

Beaumont's observations on digestion and on the state of St. Martin's stomach under various conditions created a sensation. In 1832, just before Beaumont's observations were published, the nature of gastric juice {*gaster,* stomach} and digestion in the stomach was a subject of much debate. Beaumont's careful observations went far toward solving the mystery. Like physicians of old who tasted urine when making a diagnosis, Beaumont tasted the mucous lining of the stomach and the gastric juices. He described them both as "saltish," but mucus was not at all acidic, and gastric fluid was very acidic. Beaumont collected copious amounts of gastric fluid through the fistula, and in controlled experiments he confirmed that gastric fluid digested meat, using a combination of hydrochloric acid and another active factor now known to be the enzyme pepsin.

These observations and others about motility and digestion in the stomach became the foundation of what we know about digestive physiology. Although research today is conducted more at the cellular and molecular level, researchers still create surgical fistulas in experimental animals to observe and sample the contents of the digestive tract.

Why is the digestive system—also referred to as the **gastrointestinal system** {*intestinus,* internal}—of such great interest? The reason is that gastrointestinal diseases today account for nearly 10% of the money spent on healthcare. Many of these conditions, such as heartburn, indigestion, gas, and constipation, are troublesome rather than major health risks, but their significance should not be underestimated. Go into any drugstore and look at the number of over-the-counter medications for digestive disorders to get a feel for the impact digestive diseases have on our society. In this chapter, we examine the gastrointestinal system and the remarkable way in which it transforms the food we eat into nutrients for the body's use.

ANATOMY OF THE DIGESTIVE SYSTEM

The digestive system begins with the oral cavity (mouth and pharynx), which serves as a receptacle for food (**FIG. 21.1a**). Swallowed food enters the **gastrointestinal tract (GI tract)** consisting of esophagus, stomach, small intestine, and large intestine. The portion of the GI tract running from the stomach to the anus is also called the **gut.**

Digestion, the chemical and mechanical breakdown of food, takes place primarily in the lumen of the gut. Along the way, secretions are added to ingested food by secretory epithelial cells and by *accessory glandular organs* that include salivary glands, the liver, the gallbladder, and the pancreas. The soupy mixture of food and secretions is known as **chyme.**

The GI tract is a long tube with muscular walls lined by secretory and transporting epithelium [p. 150]. At intervals along the tract, rings of muscle function as *sphincters* to separate the tube into segments with distinct functions. Food moves through the tract propelled by waves of muscle contraction.

The products of digestion are absorbed across the intestinal epithelium and pass into the interstitial fluid. From there, they move into the blood or lymph for distribution throughout the body. Any waste remaining in the lumen at the end of the GI tract leaves the body through an opening called the *anus.*

Because the digestive system opens to the outside world, the tract lumen and its contents are actually part of the external environment. (Think of a hole passing through the center of a bead.) [Fig. 1.2, p. 4] This allows an amazing variety of bacteria to live in the lumen, particularly in the large intestine. The arrangement is usually described as a *commensal* relationship, in which the bacteria benefit from having a home and food supply, while the human body is not affected. However, we are discovering ways in which the body does benefit from its bacterial companions. The relationship between humans and their bacterial *microbiome* is a hot topic in physiology today, and you will learn more about it at the end of the chapter.

RUNNING PROBLEM | Cholera in Haiti

Brooke was looking for a way to spend her 2013 winter break, so she volunteered to join a disaster relief team going to Haiti. Upon her arrival in the earthquake-devastated country, Brooke was appalled to see the living conditions. Many people were still living in tents with little or no running water and sanitation. To make matters worse, in October 2010, the World Health Organization (WHO) had issued a global outbreak alert for a cholera epidemic. *Vibrio cholerae,* the cholera bacterium, causes vomiting and massive volumes of watery diarrhea in people who consume contaminated food or water. There had been no cholera in Haiti for nearly a hundred years, but in the years since the earthquake, nearly 700,000 cases and over 8000 deaths have been reported.

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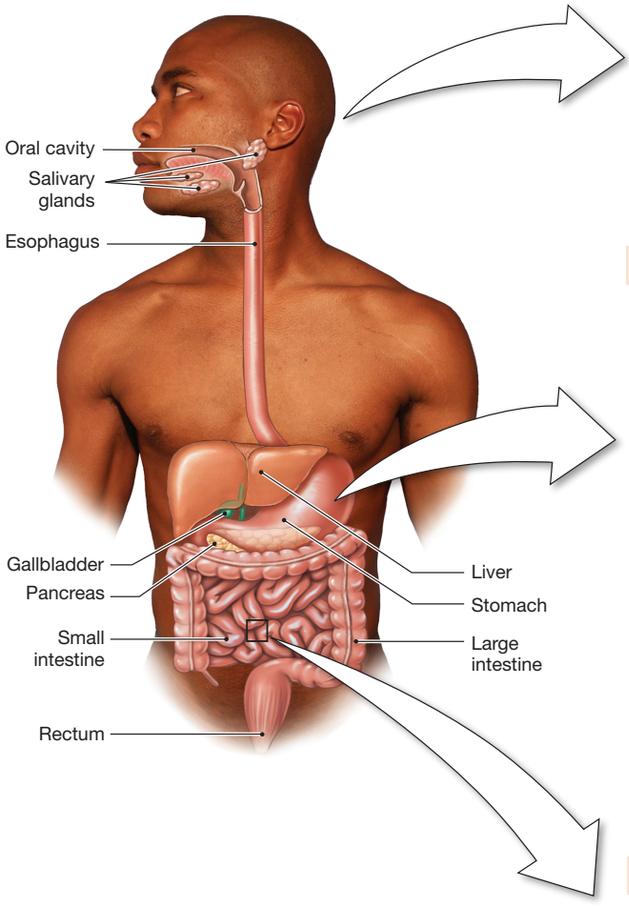
The Digestive System Is a Tube

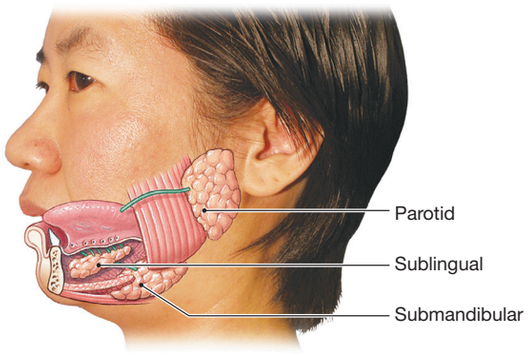
In the oral cavity, the first stages of digestion begin with chewing and the secretion of saliva by three pairs of **salivary glands:** *sublingual glands* under the tongue, *submandibular glands* under the

The Digestive System

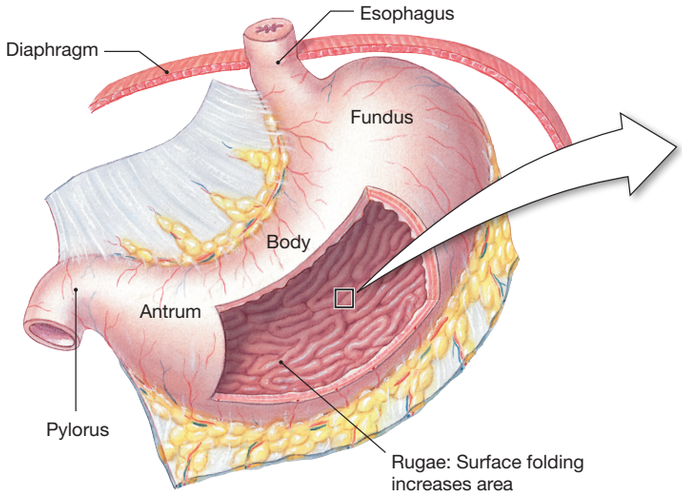
(a) Overview of the Digestive System



(b) Salivary Glands



(c) Stomach



(d) Structure of the Small Intestine

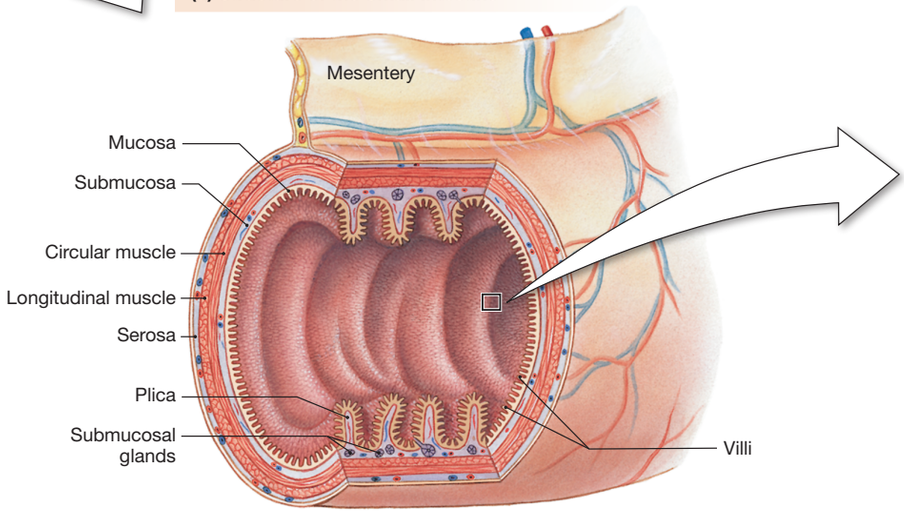
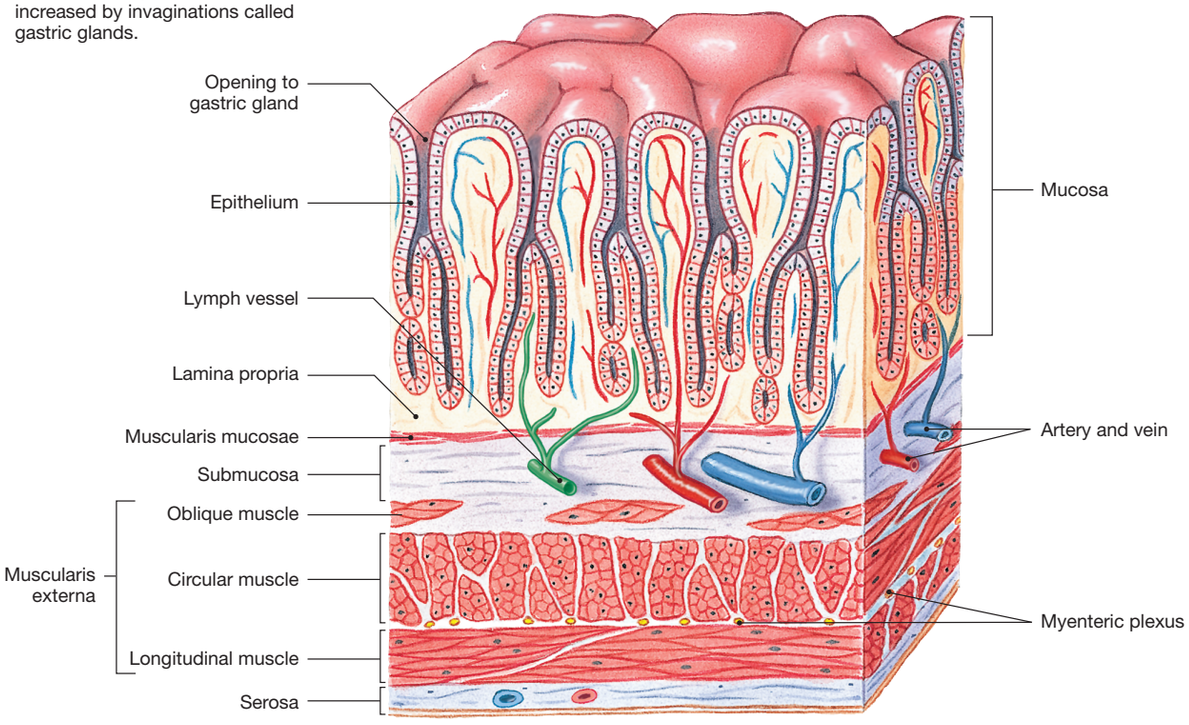


FIGURE QUESTION

Name the accessory glands and organs of the digestive system.

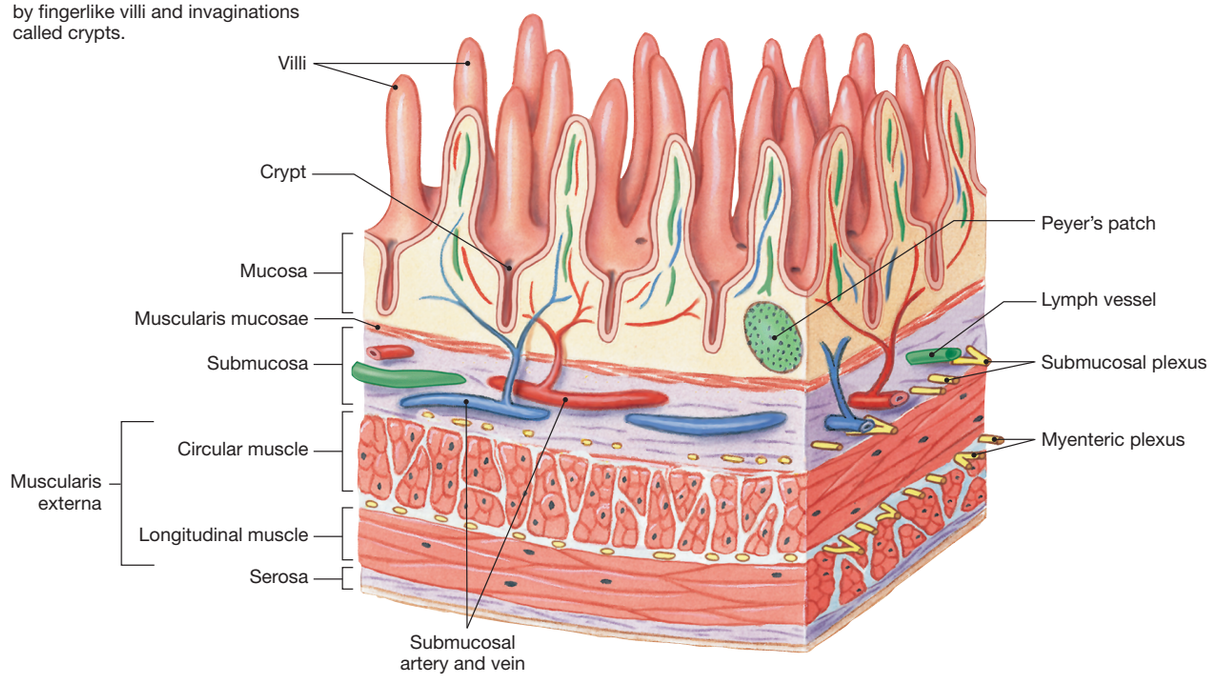
(e) Sectional View of the Stomach

In the stomach, surface area is increased by invaginations called gastric glands.



(f) Sectional View of the Small Intestine

Intestinal surface area is enhanced by fingerlike villi and invaginations called crypts.



mandible (jawbone), and *parotid glands* lying near the hinge of the jaw (Fig. 21.1b). Swallowed food passes into the **esophagus,** a narrow tube that travels through the thorax to the abdomen (Fig. 21.1a). The esophageal walls are skeletal muscle initially but transition to smooth muscle about two-thirds of the way down the length. Just below the diaphragm, the esophagus ends at the **stomach,** a baglike organ that can hold as much as 2 liters of food and fluid when fully (if uncomfortably) expanded.

The stomach has three sections: the upper **fundus,** the central **body,** and the lower **antrum** (Fig. 21.1c). The stomach continues digestion that began in the mouth by mixing food with acid and enzymes to create chyme. The **pylorus** {gatekeeper} or opening between the stomach and the **small intestine** is guarded by the **pyloric valve.** This thickened band of smooth muscle relaxes to allow only small amounts of chyme into the small intestine at any one time.

The stomach acts as an intermediary between the behavioral act of eating and the physiological events of digestion and absorption in the intestine. Integrated signals and feedback loops between the intestine and stomach regulate the rate at which chyme enters the duodenum. This ensures that the intestine is not overwhelmed with more than it can digest and absorb.

Most digestion takes place in the small intestine, which has three sections: the **duodenum** (the first 25 cm), **jejunum,** and **ileum** (the latter two together are about 260 cm long). Digestion is carried out by intestinal enzymes, aided by exocrine secretions from two accessory glandular organs: the pancreas and the liver (Fig. 21.1a). Secretions from these two organs enter the initial section of the duodenum through ducts. A tonically contracted sphincter (the *sphincter of Oddi*) keeps pancreatic fluid and bile from entering the small intestine except during a meal.

Digestion finishes in the small intestine, and nearly all digested nutrients and secreted fluids are absorbed there, leaving about 1.5 liters of chyme per day to pass into the **large intestine** (Fig. 21.1a). In the **colon**—the proximal section of the large intestine—watery chyme becomes semisolid **feces** {*faeces,* dregs} as water and electrolytes are absorbed out of the chyme and into the extracellular fluid (ECF).

When feces are propelled into the terminal section of the large intestine, known as the **rectum,** distension of the rectal wall triggers a *defecation reflex.* Feces leave the GI tract through the **anus,** with its **external anal sphincter** of skeletal muscle, which is under voluntary control.

In a living person, the digestive system from mouth to anus is about 450 cm (nearly 15 ft.) long! Of this length, 395 cm (about 13 ft.) consists of the large and small intestines. Try to imagine 13 ft. of rope ranging from 1 to 3 inches in diameter all coiled up inside your abdomen from the belly button down. The tight arrangement of the abdominal organs helps explain why you feel the need to loosen your belt after consuming a large meal.

Measurements of intestinal length made during autopsies are nearly double those given here because after death, the longitudinal muscles of the intestinal tract relax. This relaxation accounts for the wide variation in intestinal length you may encounter in different references.

The GI Tract Wall Has Four Layers

The basic structure of the gastrointestinal wall is similar in the stomach and intestines, although variations exist from one section of the GI tract to another (Fig. 21.1e, f). The gut wall is crumpled into folds to increase its surface area. These folds are called *rugae* in the stomach and *plicae* in the small intestine. The intestinal mucosa also projects into the lumen in small fingerlike extensions known as **villi** (Fig. 21.1f). Additional surface area is added by tubular invaginations of the surface that extend down into the supporting connective tissue. These invaginations are called **gastric glands** in the stomach and **crypts** in the intestine. Some of the deepest invaginations form secretory **submucosal glands** that open into the lumen through ducts.

The gut wall consists of four layers: (1) an inner *mucosa* facing the lumen, (2) a layer known as the *submucosa,* (3) layers of smooth muscle known collectively as the *muscularis externa,* and (4) a covering of connective tissue called the *serosa.*

Mucosa The **mucosa,** the inner lining of the gastrointestinal tract, has three layers: a single layer of **mucosal epithelium** facing the lumen; the **lamina propria,** subepithelial connective tissue that holds the epithelium in place; and the **muscularis mucosae,** a thin layer of smooth muscle. Several structural modifications increase the amount of mucosal surface area to enhance absorption.

1. *The mucosal epithelium* is the most variable feature of the GI tract, changing from section to section. The cells of the mucosa include transporting epithelial cells (called *enterocytes* in the small intestine), endocrine and exocrine secretory cells, and stem cells. At the *mucosal* (apical) surface of the epithelium [p. 79], cells secrete ions, enzymes, mucus, and paracrine molecules into the lumen. On the *serosal* (basolateral) surface of the epithelium, substances being absorbed from the lumen and molecules secreted by epithelial cells enter the ECF.

   The cell-to-cell junctions that tie GI epithelial cells together vary [p. 72]. In the stomach and colon, the junctions form a tight barrier so that little can pass between the cells. In the small intestine, junctions are not as tight. This intestinal epithelium is considered "leaky" because some water and solutes can be absorbed between the cells (the *paracellular pathway*) instead of through them. We now know that these junctions have plasticity and that their "tightness" and selectivity can be regulated to some extent.

   GI *stem cells* are rapidly dividing, undifferentiated cells that continuously produce new epithelium in the crypts and gastric glands. As stem cells divide, the newly formed cells are pushed toward the luminal surface of the epithelium. The average life span of a GI epithelial cell is only a few days, a good indicator of the rough life such cells lead. As with other types of epithelium, the rapid turnover and cell division rate in the GI tract make these organs susceptible to developing cancers. In 2013, cancers of the colon and rectum (colorectal cancer) were the second leading cause of cancer

deaths in the United States. The death rate has been steadily falling, however, due to more screening examinations and better treatments.

2. The *lamina propria* is subepithelial connective tissue that contains nerve fibers and small blood and lymph vessels. Absorbed nutrients pass into the blood and lymph here (Fig. 21.1e). This layer also contains wandering immune cells, such as macrophages and lymphocytes, patrolling for invaders that enter through breaks in the epithelium.

   In the intestine, collections of lymphoid tissue adjoining the epithelium form small *nodules* and larger **Peyer's patches** that create visible bumps in the mucosa (Fig. 21.1f). These lymphoid aggregations are a major part of the **gut-associated lymphoid tissue (GALT).**
3. The *muscularis mucosae,* a thin layer of smooth muscle, separates the lamina propria from the submucosa. Contraction of muscles in this layer alters the effective surface area for absorption by moving the villi back and forth, like the waving tentacles of a sea anemone.

Submucosa The **submucosa** is the middle layer of the gut wall. It is composed of connective tissue with larger blood and lymph vessels running through it (Fig. 21.1e, f). The submucosa also contains the **submucosal plexus** {*plexus,* interwoven}, one of the two major nerve networks of the **enteric nervous system** [p. 229]. The submucosal plexus (also called *Meissner's plexus*) innervates cells in the epithelial layer as well as smooth muscle of the muscularis mucosae.

Muscularis Externa The outer wall of the gastrointestinal tract, the **muscularis externa,** consists primarily of two layers of smooth muscle: an inner circular layer and an outer longitudinal layer (Fig. 21.1d, f). Contraction of the circular layer decreases the diameter of the lumen. Contraction of the longitudinal layer shortens the tube. The stomach has an incomplete third layer of oblique muscle between the circular muscles and the submucosa (Fig. 21.1e).

The second nerve network of the enteric nervous system, the **myenteric plexus** {*myo-,* muscle + *enteron,* intestine}, lies between the longitudinal and circular muscle layers. The myenteric plexus (also called *Auerbach's plexus*) controls and coordinates the motor activity of the muscularis externa.

Serosa The outer covering of the entire digestive tract, the **serosa,** is a connective tissue membrane that is a continuation of the **peritoneal membrane** (*peritoneum*) lining the abdominal cavity [p. 59]. The peritoneum also forms sheets of **mesentery** that hold the intestines in place so that they do not become tangled as they move.

The next section is a brief look at the four processes of secretion, digestion, absorption, and motility. Gastrointestinal physiology is a rapidly expanding field, and this textbook does not attempt to be all inclusive. Instead, it focuses on selected broad aspects of digestive physiology.

RUNNING **PROBLEM**

Facing a cholera epidemic in the country, members of the relief team were apprehensive. A worker from the U.S. Centers for Disease Control and Prevention (CDC) spoke to the group about proper precautions. He warned them to be careful about what they ate and drank, and to wash their hands often. Then, about five days into her trip, Brooke had a bout of copious and watery diarrhea, which she initially attributed to the emotional stress of the relief work. But when she developed dizziness and a rapid heartbeat, she went to the medical tent. There, she was diagnosed with dehydration from cholera-induced diarrhea.

Q1: *Given Brooke's watery diarrhea, what would you expect her ECF volume to be?*

Q2: *Why was Brooke experiencing a rapid heartbeat?*

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CONCEPT CHECK

1. Is the lumen of the digestive tract on the apical or basolateral side of the intestinal epithelium? On the serosal or mucosal side?
2. Name the four layers of the GI tract wall, starting at the lumen and moving out.
3. Name the structures a piece of food passes through as it travels from mouth to anus.

DIGESTIVE FUNCTION AND PROCESSES

The primary function of the digestive system is to move nutrients, water, and electrolytes from the external environment into the body's internal environment. To accomplish this, the system uses four basic processes: digestion, absorption, secretion, and motility (**FIG. 21.2**). **Digestion** is the chemical and mechanical breakdown of foods into smaller units that can be taken across the intestinal epithelium into the body. **Absorption** is the movement of substances from the lumen of the GI tract to the extracellular fluid. **Secretion** in the GI tract has two meanings. It can mean the movement of water and ions from the ECF to the digestive tract lumen (the opposite of absorption), but it can also mean the release of substances synthesized by GI epithelial cells into either the lumen or the ECF. **Motility** {*movere,* move + *tillis,* characterized by} is movement of material in the GI tract as a result of muscle contraction.

Although it might seem simple to digest and absorb food, the digestive system faces three significant challenges:

1. *Avoiding autodigestion* The food we eat is mostly in the form of macromolecules, such as proteins and complex carbohydrates, so our digestive systems must secrete powerful enzymes to digest food into molecules that are small enough to be absorbed into the body. At the same time, however, these enzymes must not digest the cells of the GI tract itself

FIG. 21.2 Four processes of the digestive system

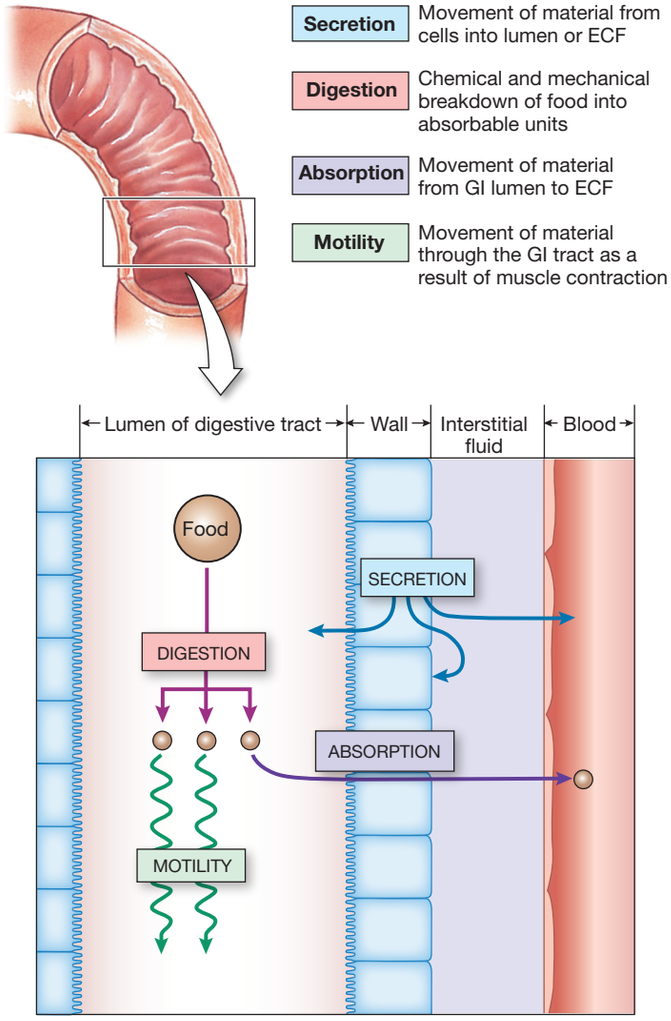
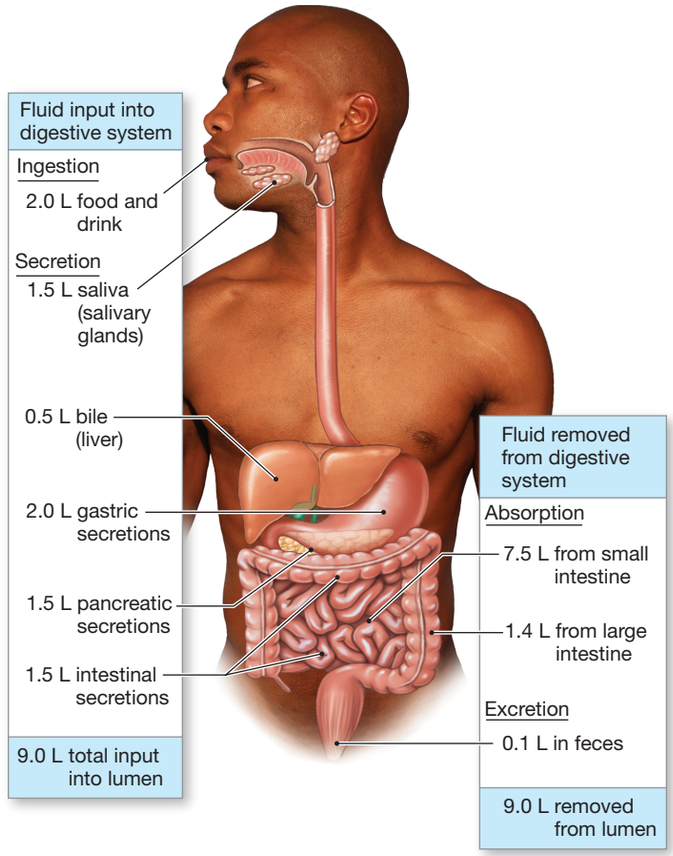


FIG. 21.3 Mass balance in the digestive system

To maintain homeostasis, the volume of fluid entering the GI tract by intake or secretion must equal the volume leaving the lumen.



(*autodigestion*). If protective mechanisms against autodigestion fail, raw patches known as *peptic ulcers* {*peptos,* digested} develop on the walls of the GI tract.

2. *Mass balance* Another challenge the digestive system faces daily is maintaining mass balance by matching fluid input with output (**FIG. 21.3**). People ingest about 2 liters of fluid a day. In addition, exocrine glands and cells secrete 7 liters or so of enzymes, mucus, electrolytes, and water into the lumen of the GI tract. That volume of secreted fluid is the equivalent of one-sixth of the body's total body water (42 liters), or more than twice the plasma volume of 3 liters. If the secreted fluid could not be reabsorbed, the body would rapidly dehydrate.
3. Normally intestinal reabsorption is very efficient, and only about 100 mL of fluid is lost in the feces. However, vomiting and diarrhea (excessively watery feces) can become an emergency when GI secretions are lost to the environment instead of being reabsorbed. In severe cases, this fluid loss can deplete extracellular fluid volume to the point that the circulatory system is unable to maintain adequate blood pressure.
4. *Defense* A final challenge the digestive system faces is protecting the body from foreign invaders. It is counterintuitive, but the largest area of contact between the body's internal environment and the outside world is in the lumen of the digestive system. As a result, the GI tract, with a total surface area about the size of a tennis court, faces daily conflict between the need to absorb water and nutrients, and the need to keep bacteria, viruses, and other pathogens from entering the body. To this end, the transporting epithelium of the GI tract is assisted by an array of physiological defense mechanisms, including mucus, digestive enzymes, acid, and the largest collection of lymphoid tissue in the body, the *gut-associated lymphoid tissue (GALT).* By one estimate, 80% of all lymphocytes [p. 514] in the body are found in the small intestine.

The human body meets these sometimes conflicting physiological challenges by coordinating motility and secretion to maximize digestion and absorption.

We Secrete More Fluid than We Ingest

In a typical day, 9 liters of fluid pass through the lumen of an adult's gastrointestinal tract—equal to the contents of three 3-liter soft drink bottles! Only about 2 liters of that volume enter the GI system through the mouth. The remaining 7 liters of fluid come from body water secreted along with ions, enzymes, and mucus (see Fig. 21.3). The ions are transported from the ECF into the lumen. Water then follows the osmotic gradient created by this transfer of solutes from one side of the epithelium to the other. Water moves through the epithelial cells via channels or through leaky junctions between cells (the paracellular pathway).

Gastrointestinal epithelial cells, like those in the kidney, are *polarized* [p. 150], with distinct apical and basolateral membranes. Each cell surface contains membrane proteins for solute and water movement, many of them similar to those of the renal tubule. The arrangement of transport proteins on the apical and basolateral membranes determines the direction of movement of solutes and water across the epithelium.

Digestive Enzymes Digestive enzymes are secreted either by exocrine glands (salivary glands and the pancreas) or by epithelial cells in the stomach and small intestine. Enzymes are proteins, which means that they are synthesized on the rough endoplasmic reticulum, packaged by the Golgi complex into secretory vesicles, and then stored in the cell until needed. On demand, they are released by exocytosis [p. 148]. Many intestinal enzymes remain bound to the apical membranes of intestinal cells, anchored by transmembrane protein "stalks" or lipid anchors [p. 64].

Some digestive enzymes are secreted in an inactive *proenzyme* form known collectively as *zymogens* [p. 100]. Zymogens must be activated in the GI lumen before they can carry out digestion. Synthesizing the enzymes in a nonfunctional form allows them to be stockpiled in the cells that make them without damaging those cells. Zymogen names often have the suffix *–ogen* added to the enzyme name, such as *pepsinogen.*

Mucus *Mucus* is a viscous secretion composed primarily of glycoproteins collectively called **mucins.** The primary functions of mucus are to form a protective coating over the GI mucosa and to lubricate the contents of the gut. Mucus is made in specialized exocrine cell called *mucous cells* in the stomach and salivary glands, and *goblet cells* in the intestine [Fig. 3.10, p. 78]. Goblet cells make up between 10% and 24% of the intestinal cell population.

The signals for mucus release include parasympathetic innervation, a variety of neuropeptides found in the enteric nervous system, and cytokines from immunocytes. Parasitic infections and inflammatory processes in the gut also cause substantial increases in mucus secretion as the body attempts to fortify its protective barrier.

CONCEPT CHECK

4. Define digestion. What is the difference between digestion and metabolism [p. 102]?
5. Why is the digestive system associated with the largest collection of lymphoid tissue in the body?
6. Draw a cell showing (1) an enzyme in a cytoplasmic secretory vesicle, (2) exocytosis of the vesicle, and (3) the enzyme remaining bound to the surface membrane of the cell rather than floating away.

Digestion and Absorption Make Food Usable

Most GI secretions facilitate digestion. The GI system digests macromolecules into absorbable units using a combination of mechanical and chemical breakdown. Chewing and churning create smaller pieces of food with more surface area exposed to digestive enzymes. The pH at which different digestive enzymes function best [p. 100] reflects the location where they are most active. For example, enzymes that act in the stomach work well at acidic pH, and those that are secreted into the small intestine work best at alkaline pH.

Most absorption takes place in the small intestine, with additional absorption of water and ions in the large intestine. Absorption, like secretion, uses many of the same transport proteins as the kidney tubule. Once absorbed, nutrients enter the blood or the lymphatic circulation.

Motility: GI Smooth Muscle Contracts Spontaneously

Motility in the gastrointestinal tract serves two purposes: moving food from the mouth to the anus and mechanically mixing food to break it into uniformly small particles. This mixing maximizes exposure of the particles to digestive enzymes by increasing particle surface area. Gastrointestinal motility is determined by the properties of the GI smooth muscle and is modified by chemical input from nerves, hormones, and paracrine signals.

Most of the gastrointestinal tract is composed of single-unit smooth muscle, with groups of cells electrically connected by gap junctions [p. 405] to create contracting segments. Different regions exhibit different types of contraction. **Tonic contractions** are sustained for minutes or hours. They occur in some smooth muscle sphincters and in the anterior portion of the stomach. **Phasic contractions,** with contraction-relaxation cycles lasting only a few seconds, occur in the posterior region of the stomach and in the small intestine.

Cycles of smooth muscle contraction and relaxation are associated with cycles of depolarization and repolarization known as **slow wave potentials** or simply *slow waves* (**FIG. 21.4a**). Current research indicates that slow waves originate in a network of cells called the **interstitial cells of Cajal** (named after the Spanish neuroanatomist Santiago Ramón y Cajal), or ICCs. These modified smooth muscle cells lie between smooth muscle layers and the intrinsic nerve plexuses, and they may act as an intermediary between the neurons and smooth muscle.

Gastrointestinal Motility

(a) Slow waves are spontaneous depolarizations in GI smooth muscle.

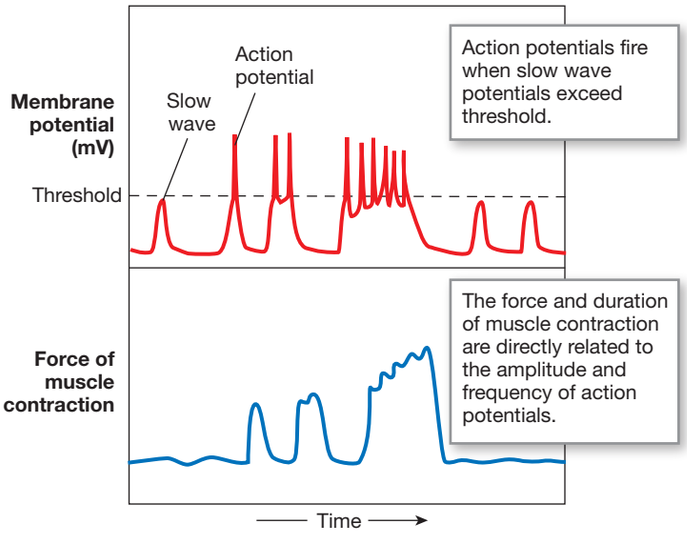
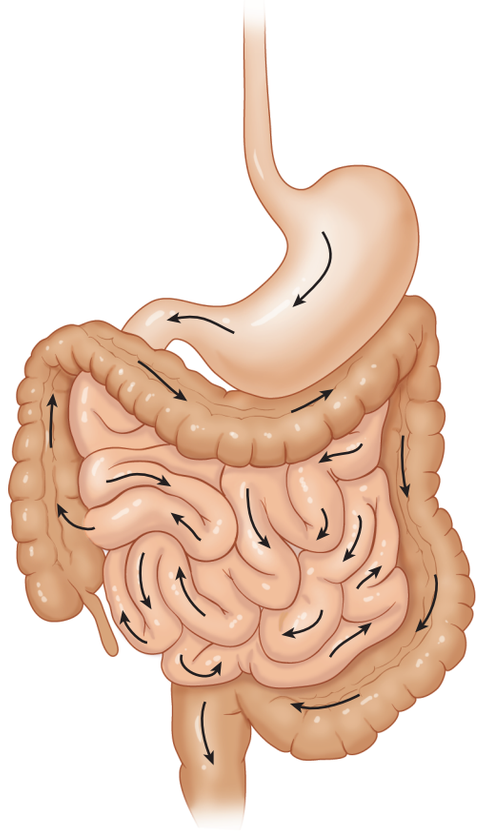


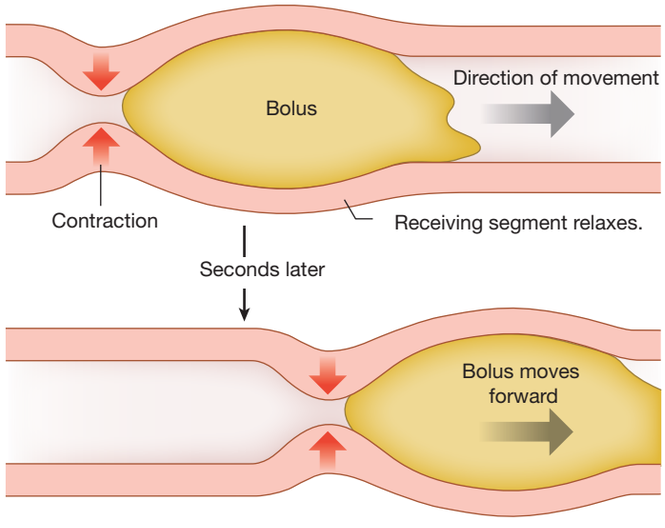
FIGURE QUESTION

Why do the peaks of the contraction waves occur after the peaks of the action potentials?

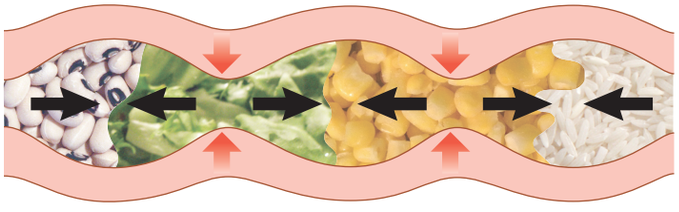
(b) The **migrating motor complex** (MMC) is a series of contractions that begin in the empty stomach and end in the large intestine.



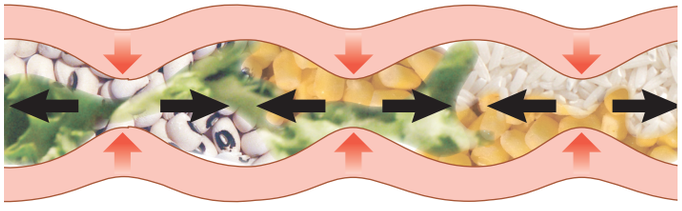
(c) Peristaltic contractions are responsible for forward movement.



(d) Segmental contractions are responsible for mixing.



Alternate segments contract, and there is little or no net forward movement.



It appears that ICCs function as the pacemakers for slow wave activity in different regions of the GI tract, just as cells of the cardiac conduction system act as pacemakers for the heart [p. 455]. Slow wave potentials differ from myocardial pacemaker potentials in that the GI waves occur at a much slower frequency (3–12 waves/min GI versus 60–90 waves/min myocardial). In addition, slow wave frequency varies by region of the digestive tract, ranging from 3 waves/min in the stomach to 12 waves/min in the duodenum.

Slow waves that begin spontaneously in ICCs spread to adjacent smooth muscle layers through gap junctions. Just as in the cardiac conducting system, the fastest pacemaker in a group of ICCs sets the pace for the entire group [p. 456]. The observation that ICCs seem to coordinate GI motility now has researchers working to establish a link between ICCs and functional bowel disorders, such as irritable bowel syndrome and chronic constipation.

One difference between slow waves and cardiac pacemaker potentials is that slow waves do not reach threshold with each cycle, and a slow wave that does not reach threshold will not cause muscle contraction. When a slow wave potential does reach threshold, voltage-gated Ca^{2+} channels in the muscle fiber open, Ca^{2+} enters, and the cell fires one or more action potentials. The depolarization phase of the slow wave action potential, like that in myocardial autorhythmic cells, is the result of Ca^{2+} entry into the cell. In addition, Ca^{2+} entry initiates muscle contraction [p. 407].

Contraction of smooth muscle, like that of cardiac muscle, is graded according to the amount of Ca^{2+} that enters the fiber. The longer the duration of the slow wave, the more action potentials fire, and the greater the contraction force in the muscle. The likelihood of a slow wave firing an action potential depends primarily on input from the enteric nervous system.

GI Smooth Muscle Exhibits Different Patterns of Contraction

Muscle contractions in the gastrointestinal tract occur in three patterns that bring about different types of movement within the tract. Between meals, when the tract is largely empty, a series of contractions begins in the stomach and passes slowly from section to section, each series taking about 90 minutes to reach the large intestine. This pattern, known as the **migrating motor complex,** is a "housekeeping" function that sweeps food remnants and bacteria out of the upper GI tract and into the large intestine (Fig. 21.4b).

Muscle contractions during and following a meal fall into one of two other patterns. (Fig. 21.4) **Peristalsis** {*peri-*, surrounding + *stalsis,* contraction} is progressive waves of contraction that move from one section of the GI tract to the next, just like the human "waves" that ripple around a football stadium or basketball arena. In peristalsis, circular muscles contract just behind a mass, or **bolus,** of food (Fig. 21.4c). This contraction pushes the bolus forward into a *receiving segment,* where the circular muscles are relaxed. The receiving segment then contracts, continuing the forward movement.

Peristaltic contractions push a bolus forward at speeds between 2 and 25 cm/sec. Peristalsis in the esophagus propels material from pharynx to stomach. Peristalsis contributes to food mixing in the stomach but in normal digestion, intestinal peristaltic waves are limited to short distances.

In **segmental contractions,** short (1–5 cm) segments of intestine alternately contract and relax (Fig. 21.4d). In the contracting segments, circular muscles contract while longitudinal muscles relax. These contractions may occur randomly along the intestine or at regular intervals. Alternating segmental contractions churn the intestinal contents, mixing them and keeping them in contact with the absorptive epithelium. When segments contract sequentially, in an oral-to-aboral direction {*ab-*, away}, intestinal contents are propelled short distances.

Motility disorders are among the more common gastrointestinal problems. They range from esophageal spasms and delayed gastric (stomach) emptying to constipation and diarrhea. *Irritable bowel syndrome* is a chronic functional disorder characterized by altered bowel habits and abdominal pain.

CONCEPT CHECK

7. What is the difference between absorption and secretion?
8. How do fats absorbed into the lymphatic system get into the general circulation for distribution to cells? [*Hint:* p. 499]
9. Why are some sphincters of the digestive system tonically contracted?

CLINICAL FOCUS

Diabetes: Delayed Gastric Emptying

Diabetes mellitus has an impact on almost every organ system. The digestive tract is not exempt. One problem that plagues more than a third of all people with diabetes is *gastroparesis,* also called delayed gastric emptying. In these patients, the migrating motor complex is absent between meals, and the stomach empties very slowly after meals. Many patients suffer nausea and vomiting as a result. The causes of diabetic gastroparesis are unclear, but recent studies of animal models and human patients show loss or dysfunction of the interstitial cells of Cajal, which serve as pacemakers and as a link between GI smooth muscle and the enteric and autonomic nervous systems. Adopting the cardiac model of an external pacemaker, scientists are now testing an implantable gastric pacemaker to promote gastric motility in diabetic patients with severe gastroparesis.

REGULATION OF GI FUNCTION

Of the four GI processes, motility and secretion are the primary regulated functions. If food moves through the system too rapidly, there will not be enough time for everything in the lumen to be digested and absorbed. Secretion is regulated so that the appropriate digestive enzymes can break down food into an absorbable form. Digestion in turn depends on motility and secretion.

Scientists used to believe that nutrient absorption was not regulated and that "what you eat is what you get." Now, however, evidence indicates that some nutrient absorption can be altered in response to long-term environmental changes.

The Enteric Nervous System Can Act Independently

The enteric nervous system (ENS) was first recognized more than a century ago, when scientists noted that isolated sections of intestine removed from the body created a reflex wave of peristaltic contraction when pressure in the lumen increased. What they observed was the ability of the ENS to carry out a reflex independent of control by the central nervous system (CNS).

In this respect, the ENS is much like the nerve networks of jellyfish and sea anemones (phylum Cnidaria) [p. 275]. You might have seen sea anemones being fed at an aquarium. As a piece of shrimp or fish drifts close to the tentacles, they begin to wave, picking up chemical "odors" through the water. Once the food contacts the tentacles, it is directed toward the mouth, passed from one tentacle to another until it disappears into the digestive cavity.

This purposeful reflex is accomplished without a brain, eyes, or a nose. The anemone's nervous system consists of a nerve network with sensory neurons, interneurons, and efferent neurons that control the muscles and secretory cells of the anemone's body. The neurons of the Cnidarian network are linked in a way that allows them to integrate information and act on it. In the same way that an anemone captures its food, the human ENS receives stimuli and acts on them. The enteric nervous system controls motility, secretion, and growth of the digestive tract.

Anatomically and functionally, the ENS shares many features with the CNS:

1. *Intrinsic neurons.* The **intrinsic neurons** of the two nerve plexuses of the digestive tract are those neurons that lie completely within the wall of the gut, just as interneurons are completely contained within the CNS. Autonomic neurons that bring signals from the CNS to the digestive system are called **extrinsic neurons.**
2. *Neurotransmitters and neuromodulators.* ENS neurons release more than 30 neurotransmitters and neuromodulators, most of which are identical to molecules found in the brain. These neurotransmitters are sometimes called *nonadrenergic, noncholinergic* to distinguish them from the traditional autonomic neurotransmitters norepinephrine and acetylcholine. Among the best known GI neurotransmitters and neuromodulators are serotonin, vasoactive intestinal peptide, and nitric oxide.
3. *Glial support cells.* The glial cells of neurons within the ENS are more similar to astroglia of the brain than to Schwann cells of the peripheral nervous system.
4. *Diffusion barrier.* The capillaries that surround ganglia in the ENS are not very permeable and create a diffusion barrier that is similar to the blood-brain barrier of cerebral blood vessels.
5. *Integrating center.* As noted earlier, reflexes that originate in the GI tract can be integrated and acted on without neural signals leaving the ENS. For this reason, the neuron network of the ENS is its own integrating center, much like the brain and spinal cord.

It was once thought that if we could explain how the ENS integrates simple behaviors, we could use the system as a model for CNS function. But studying ENS function is difficult because enteric reflexes have no discrete command center. Instead, in an interesting twist, GI physiologists are applying information gleaned from studies of the brain and spinal cord to investigate ENS function. The complex interactions between the enteric and central nervous systems, the endocrine system, and the immune system promise to provide scientists with questions to investigate for many years to come.

Short Reflexes Integrate in the Enteric Nervous System

The enteric nerve plexuses in the gut wall act as a "little brain," allowing local reflexes to begin, be integrated, and end completely in the GI tract (**FIG. 21.5**, red arrows). Reflexes that originate within the enteric nervous system and are integrated there without outside input are called **short reflexes.** The submucosal plexus contains sensory neurons that receive signals from the lumen of the gut. The ENS network integrates this sensory information, then initiates responses. The submucosal plexus controls secretion by GI epithelial cells. Myenteric plexus neurons in the muscularis externa influence motility.

Long Reflexes Integrate in the CNS

Although the ENS can work in isolation, it also sends sensory information to the CNS and receives input from the CNS through autonomic neurons. A classic neural reflex begins with a stimulus transmitted along a sensory neuron to the CNS, where the stimulus is integrated and acted on. In the digestive system, some classic reflexes originate with sensory receptors in the GI tract, but others originate outside the digestive system (Fig. 21.5, gray arrows). No matter where they originate, digestive reflexes integrated in the CNS are called **long reflexes.**

Long reflexes that originate outside the digestive system include feedforward reflexes [p. 17] and emotional reflexes. These reflexes are called **cephalic reflexes** because they originate in the brain {*cephalicus,* head}. *Feedforward reflexes* begin with stimuli such as the sight, smell, sound, or thought of food, and they prepare the digestive system for food that the brain is anticipating. For example, if you are hungry and smell dinner cooking, your mouth waters and your stomach growls.

FIG. 21.5 Integration of digestive reflexes

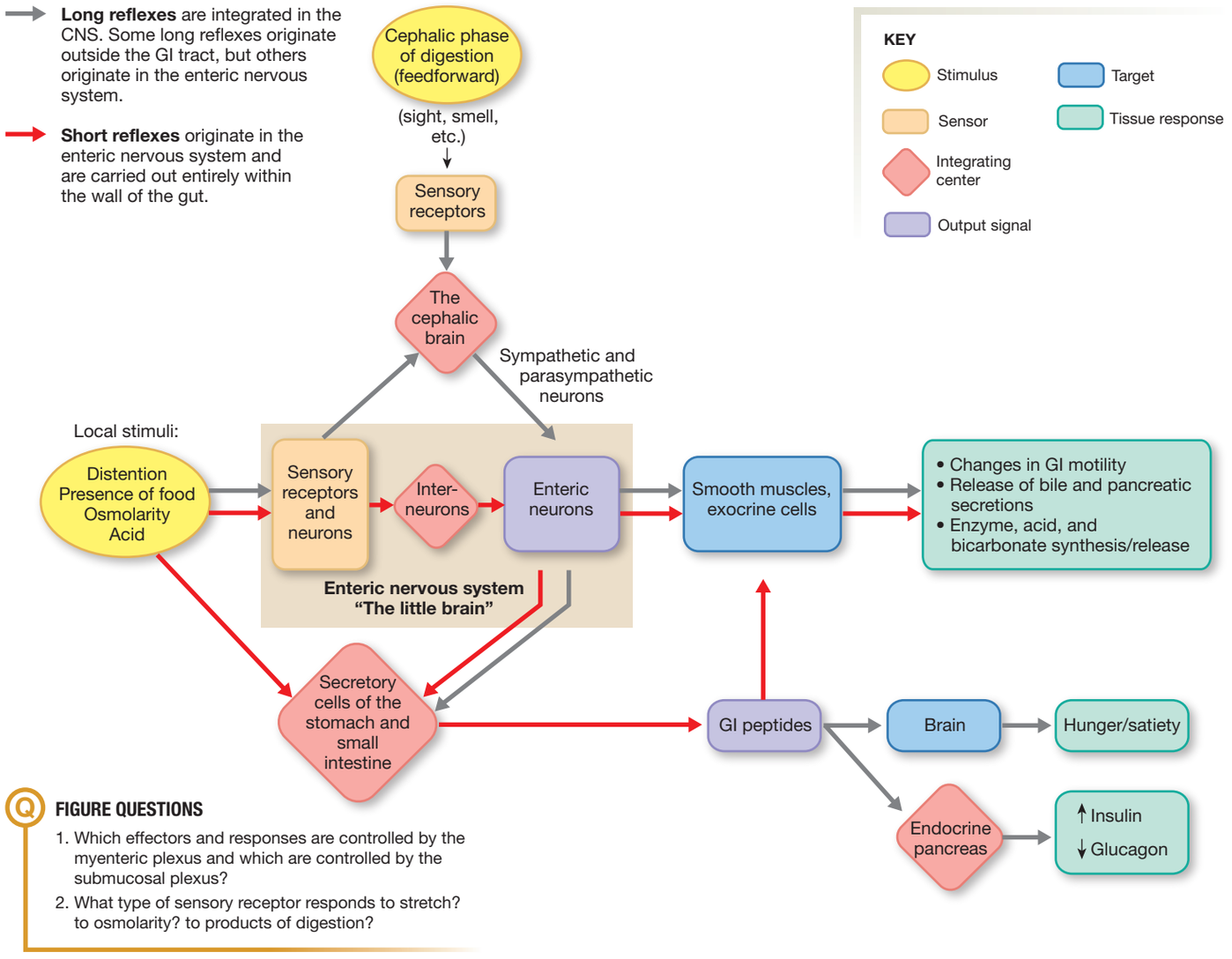


FIGURE QUESTIONS

1. Which effectors and responses are controlled by the myenteric plexus and which are controlled by the submucosal plexus?
2. What type of sensory receptor responds to stretch? to osmolarity? to products of digestion?

Emotional reflexes and their influence on the GI tract illustrate another link between the brain and the digestive system. GI responses to emotions range from traveler's constipation to "butterflies in the stomach" to psychologically induced vomiting and diarrhea.

In long reflexes, the smooth muscle and glands of the GI tract are under autonomic control. In general, we say that the parasympathetic division is excitatory and enhances GI functions, leading to its nickname of "rest and digest." Most parasympathetic neurons to the GI tract are found in the vagus nerve. Sympathetic neurons usually inhibit GI function.

CONCEPT CHECK

10. Excitation of GI function by the parasympathetic division and inhibition by the sympathetic division is an example of what kind of control?

GI Peptides Include Hormones, Neuropeptides, and Cytokines

Peptides secreted by cells of the digestive tract may act as hormones or paracrine signals. Some of these GI peptides were first identified and named in other body systems. Because their names have nothing to do with their function in the gastrointestinal system, learning the terminology can be challenging.

In the digestive system, GI peptides excite or inhibit motility and secretion. Some paracrine peptides are secreted into the lumen, where they combine with receptors on the apical membrane of the luminal epithelium to elicit a response. Others are secreted into the extracellular fluid where they diffuse short distances to act on neighboring cells.

GI peptides also act outside the GI tract, and some of their most interesting actions involve the brain. For example, in experimental studies the GI hormone **cholecystokinin (CCK)** enhances *satiety,* the

feeling that hunger has been satisfied. However, CCK is also manufactured by neurons and functions as a neurotransmitter in the brain, so it is difficult to determine how much of the normal satiety response is due to CCK from the gut. Another GI peptide, *ghrelin,* is secreted by the stomach and acts on the brain to increase food intake.

Researchers have now sequenced more than 30 peptides from the GI mucosa, but only some of them are widely accepted as hormones. A few peptides have well-defined paracrine effects, but most fall into a long list of candidate hormones. In addition, we know of nonpeptide regulatory molecules, such as histamine, that function as paracrine signals. Because of the uncertainty associated with the field, we restrict our focus in this chapter to the major regulatory molecules.

GI Hormones GI hormones, like all hormones, are secreted into the blood and transported throughout the body. They act on the GI tract, on accessory organs such as the pancreas, and on distant targets, such as the brain.

The hormones of the gastrointestinal tract occupy an interesting place in the history of endocrinology. In 1902, two English physiologists, W. M. Bayliss and E. H. Starling, discovered that acidic chyme entering the small intestine from the stomach caused the release of pancreatic juices even when all nerves to the pancreas were cut. Because the only communication remaining between intestine and pancreas was the blood supply that ran between them, Bayliss and Starling postulated the existence of some blood-borne (*humoral*) factor released by the intestine.

When duodenal extracts applied directly to the pancreas stimulated secretion, they knew they were dealing with a chemical produced by the duodenum. They named the substance *secretin.* Starling further proposed that the general name *hormone,* from the Greek word meaning "I excite," be given to all humoral agents that act at a site distant from their release.

In 1905, J. S. Edkins postulated the existence of a gastric hormone that stimulated gastric acid secretion. It took more than 30 years for researchers to isolate a relatively pure extract of the gastric hormone, and it was 1964 before the hormone, named *gastrin,* was finally purified.

Why was research on the digestive hormones so slow to develop? A major reason is that GI hormones are secreted by isolated endocrine cells scattered among other cells of the mucosal epithelium. At one time, the only way to obtain these hormones was to make a crude extract of the entire epithelium, a procedure that also liberated digestive enzymes and paracrine molecules made in adjacent cells. For this reason, it was very difficult to tell whether the physiological effect elicited by the extract came from one hormone, from more than one hormone, or from a paracrine signal such as histamine.

GI Hormone Families The gastrointestinal hormones are usually divided into three families. All the members of a family have similar amino acid sequences, and in some cases there is overlap in their ability to bind to receptors. The sources, targets, and effects of the major GI hormones are summarized in **TABLE 21.1**.

TABLE 21.1 The GI Hormones

	Stimulus for Release	Primary Target(s)	Primary Effect(s)	Other Information
Stomach				
Gastrin (G Cells)	Peptides and amino acids; neural reflexes	ECL cells and parietal cells	Stimulates gastric acid secretion and mucosal growth	Somatostatin inhibits release.
Intestine				
Cholecystokinin (CCK)	Fatty acids and some amino acids	Gallbladder, pancreas, stomach	• Stimulates gallbladder contraction and pancreatic enzyme secretion • Inhibits gastric emptying and acid secretion	• Promotes satiety • Some effects may be due to CCK as a neurotransmitter.
Secretin	Acid in small intestine	Pancreas, stomach	• Stimulates HCO_3^- secretion • Inhibits gastric emptying and acid secretion	
Motilin	Fasting: periodic release every 1.5–2 hours	Gastric and intestinal smooth muscle	Stimulates migrating motor complex	Inhibited by eating a meal
Gastric Inhibitory Peptide (GIP)	Glucose, fatty acids, and amino acids in small intestine	Beta cells of pancreas	• Stimulates insulin release (feedforward mechanism) • Inhibits gastric emptying and acid secretion	
Glucagon-Like Peptide-1 (GLP-1)	Mixed meal that includes carbohydrates or fats in the lumen	Endocrine pancreas	• Stimulates insulin release • Inhibits glucagon release and gastric function	Promotes satiety

The *gastrin family* includes the hormones **gastrin** and *cholecystokinin* (CCK), plus several variants of each. Their structural similarity means that gastrin and CCK can bind to and activate the same CCKB receptor.

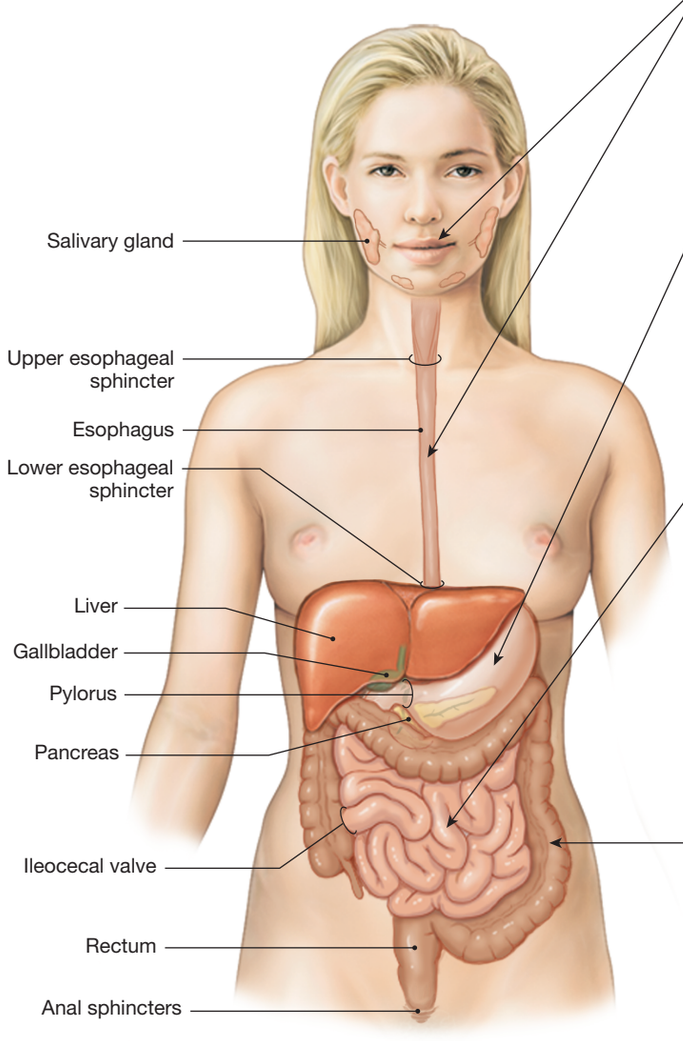
The *secretin family* includes **secretin; vasoactive intestinal peptide (VIP),** a nonadrenergic-noncholinergic neurotransmitter; and **GIP,** a hormone known originally as *gastric inhibitory peptide* because it inhibited gastric acid secretion in early experiments. Subsequent studies, however, indicated that GIP administered in lower physiological doses does not block acid secretion. Researchers proposed a new name with the same initials—**glucose-dependent insulinotropic peptide**—that more accurately describes the hormone's action: it stimulates insulin release in response to glucose in the intestinal lumen. However, for the most part *gastric inhibitory peptide* has remained the preferred name.

Another member of the secretin family is the hormone **glucagon-like peptide-1** (GLP-1). GIP and GLP-1 act together as feedforward signals for insulin release, as you will learn when you study the endocrine pancreas [Chapter 22].

The third family of peptides contains those that do not fit into the other two families. The primary member of this group is the hormone **motilin.** Increases in motilin secretion are associated with the migrating motor complex.

In the remainder of this chapter, we integrate motility, secretion, digestion, and absorption as we follow food passing through the GI tract. **FIGURE 21.6** is a summary of the main events that occur in each section of the GI tract. Food processing traditionally is divided into three phases: a cephalic phase, a gastric phase, and an intestinal phase.

FIG. 21.6 Overview of digestive function



Oral Cavity and Esophagus	
Secretion	Saliva (salivary glands)
Digestion	Carbohydrates
Absorption	None
Motility	Chewing. Swallowing.

Stomach	
Secretion	HCl (parietal cells). Pepsinogen and gastric lipase (chief cells). Mucus and bicarbonate (surface mucous cells). Gastrin (G cells). Histamine (ECL cells).
Digestion	Proteins. Fats (minimal).
Absorption	Lipid-soluble substances such as alcohol and aspirin
Motility	Peristaltic mixing and propulsion

Small Intestine	
Secretion	Enzymes (enterocytes). Mucus (goblet cells). Hormones: CCK, secretin, GIP, and others (endocrine cells). Enzymes and bicarbonate (exocrine pancreas). Bile (liver, stored in gallbladder).
Digestion	Polypeptides. Carbohydrates. Fats. Nucleic Acids.
Absorption	Amino acids and small peptides. Monosaccharides. Fatty acids, monoglycerides, cholesterol. Nitrogenous bases. Water. Ions, minerals, vitamins.
Motility	Mixing and propulsion primarily by segmentation. Some peristalsis.

Large Intestine	
Secretion	Mucus (goblet cells)
Digestion	None (except by bacteria)
Absorption	Ions, minerals, vitamins. Water. Small organic molecules made by gut bacteria.
Motility	Segmental mixing. Mass movement for propulsion.

INTEGRATED FUNCTION: THE CEPHALIC PHASE

Digestive processes in the body begin before food ever enters the mouth. Simply smelling, seeing, or even *thinking* about food can make our mouths water and our stomachs rumble. These long reflexes that begin in the brain create a feedforward response known as the **cephalic phase** of digestion.

Anticipatory stimuli and the stimulus of food in the oral cavity activate neurons in the medulla oblongata. The medulla in turn sends an efferent signal through autonomic neurons to the salivary glands, and through the vagus nerve to the enteric nervous system. In response to these signals, the stomach, intestine, and accessory glandular organs begin secretion and increase motility in anticipation of the food to come.

Chemical and Mechanical Digestion Begins in the Mouth

When food first enters the mouth, it is met by a flood of the secretion we call *saliva.* Saliva has four important functions:

1. *Soften and moisten food.* The water and mucus in saliva soften and lubricate food to make it easier to swallow. You can appreciate this function if you have ever tried to swallow a dry soda cracker without chewing it thoroughly.
2. *Digestion of starch.* Chemical digestion begins with the secretion of *salivary amylase.* Amylase breaks starch into maltose after the enzyme is activated by Cl^- in saliva. If you chew on an unsalted soda cracker for a long time, you may be able to detect the conversion of the cracker's flour starch to maltose, which is sweeter.
3. *Taste.* Saliva dissolves food so that we can taste it [p. 325].
4. *Defense.* The final function of saliva is defense. *Lysozyme* is an antibacterial salivary enzyme, and salivary *immunoglobulins* disable bacteria and viruses. In addition, saliva helps wash the teeth and keep the tongue free of food particles.

Mechanical digestion of food begins in the oral cavity with chewing. The lips, tongue, and teeth all contribute to the **mastication** {*masticare,* to chew} of food, creating a softened, moistened mass (*bolus*) that can be easily swallowed.

Saliva Is an Exocrine Secretion

Saliva is a complex hyposmotic fluid that contains water, ions, mucus, and proteins such as enzymes and immunoglobulins. Three pairs of salivary glands produce as much as 1.5 liters of saliva a day. Salivary glands are exocrine glands, with secretory epithelium arranged in grape-like clusters of cells called **acini** {*acinus,* grape or berry}. Each acinus surrounds a duct, and the individual ducts join to form larger and larger ducts (like the stems on a bunch of grapes). The main excretory duct of each gland empties into the mouth.

Secretions from the three pairs of salivary glands vary in composition. The parotid glands produce a watery solution of enzymes while sublingual glands produce a mucus-rich saliva. Secretions from the submandibular glands are mixed, with both mucus and enzymes.

The production of saliva is a two-step process. The initial fluid secreted by the acinar cells resembles extracellular fluid in its ionic composition: an isotonic NaCl solution. As this fluid passes through the duct on its way to the oral cavity, epithelial cells along the duct reabsorb NaCl and secrete K^+ and bicarbonate ion until the ion ratio in the duct fluid is more like that of intracellular fluid (high in K^+ and low in Na^+). The apical membranes of the duct cells have very low water permeability, and the net removal of solute from the secreted fluid results in saliva that is hyposmotic to plasma.

Salivation is under autonomic control and can be triggered by multiple stimuli, including the sight, smell, touch, and even thought of food. Parasympathetic innervation is the primary stimulus for secretion of saliva, but there is also some sympathetic innervation to the glands. In ancient China, a person suspected of a crime was sometimes given a mouthful of dry rice to chew during questioning. If he could produce enough saliva to moisten the rice and swallow it, he went free. If his nervous state dried up his salivary reflex, however, he was pronounced guilty. Recent research has confirmed that stress, such as that associated with lying or anxiety from being questioned, decreases the volume of salivary secretion.

CONCEPT CHECK **11.** How do mucin, amylase, and immunoglobulins move from salivary gland epithelial cells into the lumen of the gland? (*Hint:* They are all proteins.)

Swallowing Moves Food from Mouth to Stomach

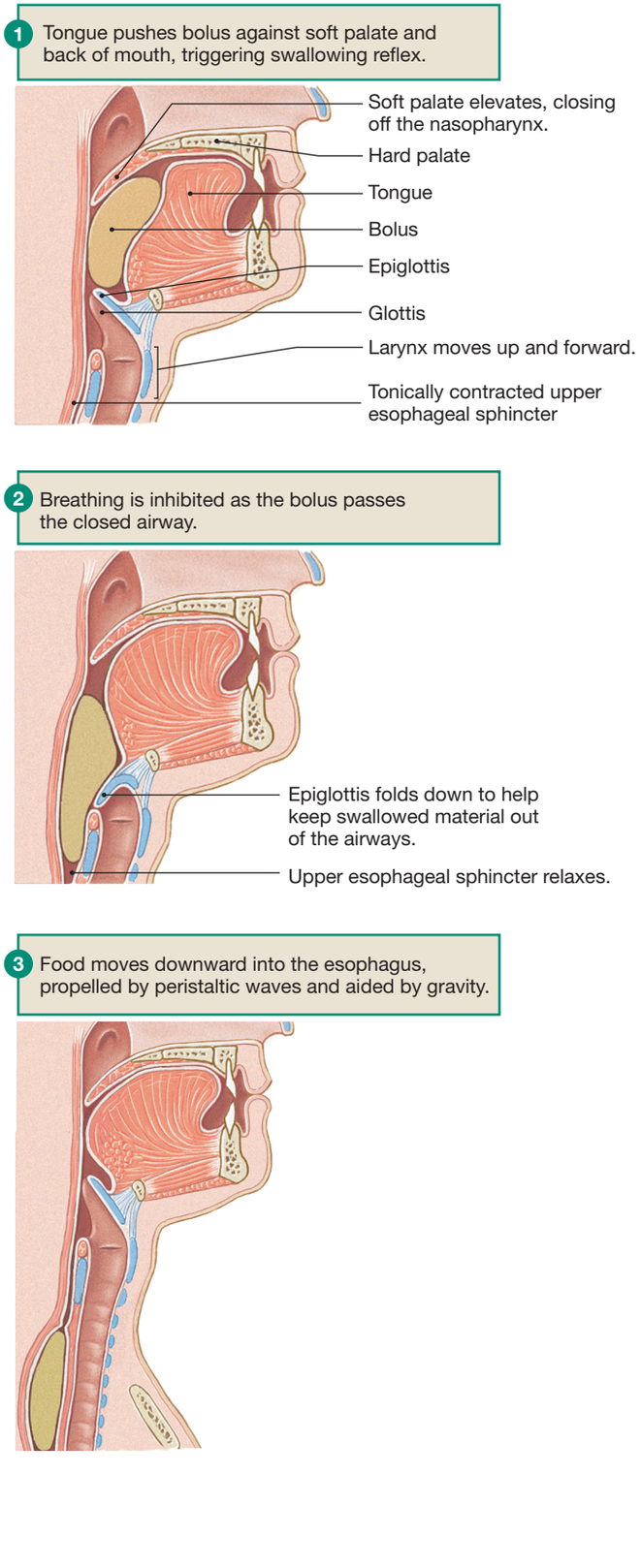
Swallowing, or **deglutition** {*glutire,* to swallow}, is a reflex action that pushes a bolus of food or liquid into the esophagus (**FIG. 21.7**). The stimulus for swallowing is pressure created when the tongue pushes the bolus against the soft palate and the back of the mouth. Pressure from the bolus activates sensory neurons that run through the *glossopharyngeal nerve* (cranial nerve IX) to a swallowing center in the medulla oblongata.

Output from the swallowing center consists of somatic motor neurons that control the skeletal muscles of the pharynx and upper esophagus as well as autonomic neurons that act on the lower portions of the esophagus. As the swallowing reflex begins, the soft palate elevates to close off the nasopharynx. Muscle contractions move the larynx up and forward, which helps close off the trachea and open the upper esophageal sphincter.

As the bolus moves down toward the esophagus, the **epiglottis** folds down, completing closure of the upper airway and preventing food and liquid from entering the airways. At the same time, respiration is briefly inhibited. When the bolus reaches the esophagus, the upper esophageal sphincter relaxes. Waves of peristaltic contractions then push the bolus toward the

FIG. 21.7 Deglutition: The swallowing reflex

Swallowing is integrated in the medulla oblongata. Sensory afferents in cranial nerve IX and somatic motor and autonomic neurons mediate the reflex.



stomach, aided by gravity. Gravity is not required, however, as you know if you have ever participated in the party trick of swallowing while standing on your head.

The lower end of the esophagus lies just below the diaphragm and is separated from the stomach by the lower esophageal sphincter. This area is not a true sphincter but a region of relatively high muscle tension that acts as a barrier between the esophagus and the stomach. When food is swallowed, the tension relaxes, allowing the bolus to pass into the stomach.

If the lower esophageal sphincter does not stay contracted, gastric acid and pepsin can irritate the lining of the esophagus, leading to the pain and irritation of *gastroesophageal reflux* {*re-*, backward + *fluxus,* flow}, more commonly called heartburn. During the inspiratory phase of breathing, when the intrapleural pressure falls, the walls of the esophagus expand [p. 549]. This expansion creates subatmospheric pressure in the esophageal lumen and can suck acidic contents out of the stomach if the sphincter is relaxed. The churning action of the stomach when filled with food can also squirt acid back into the esophagus if the sphincter is not fully contracted. *Gastroesophageal reflux disorder* or GERD is one the most common digestive disorders in American society.

INTEGRATED FUNCTION: THE GASTRIC PHASE

About 3.5 liters of food, drink, and saliva enter the fundus of the stomach each day. The stomach has three general functions:

1. **Storage.** The stomach stores food and regulates its passage into the small intestine, where most digestion and absorption take place.
2. **Digestion.** The stomach chemically and mechanically digests food into the soupy mixture of uniformly small particles called chyme.
3. **Defense.** The stomach protects the body by destroying many of the bacteria and other pathogens that are swallowed with food or trapped in airway mucus. At the same time, the stomach must protect itself from being damaged by its own secretions.

Before food even arrives, digestive activity in the stomach begins with the long **vagal reflex** of the cephalic phase (**FIG. 21.8**). Then, once food enters the stomach, stimuli in the gastric lumen initiate a series of short reflexes that constitute the **gastric phase** of digestion.

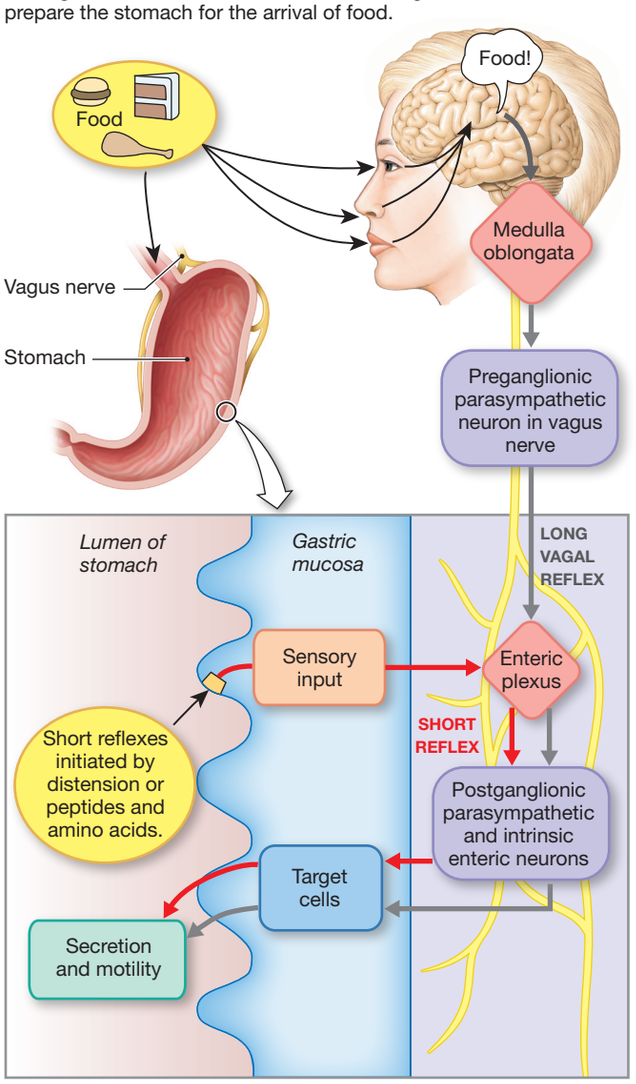
In gastric phase reflexes, distension of the stomach and the presence of peptides or amino acids in the lumen activate endocrine cells and enteric neurons. Hormones, neurotransmitters, and paracrine molecules then influence motility and secretion.

The Stomach Stores Food

When food arrives from the esophagus, the stomach relaxes and expands to hold the increased volume. This neurally mediated reflex is called *receptive relaxation.* The upper half of the stomach remains relatively quiet, holding food until it is ready to be digested. The storage function of the stomach is perhaps the least

FIG. 21.8 Cephalic and gastric phase reflexes

The sight, smell, and taste of food initiate long reflexes that prepare the stomach for the arrival of food.



obvious aspect of digestion. However, whenever we ingest more than we need from a nutritional standpoint, the stomach must regulate the rate at which food enters the small intestine.

Without such regulation, the small intestine would not be able to digest and absorb the load presented to it, and significant amounts of unabsorbed chyme would pass into the large intestine. The epithelium of the large intestine is not designed for large-scale nutrient absorption, so most of the chyme would become feces, resulting in diarrhea. This "dumping syndrome" is one of the less pleasant side effects of surgery that removes portions of either the stomach or small intestine.

While the upper stomach is quietly holding food, the lower stomach is busy with digestion. In the distal half of the stomach, a series of peristaltic waves pushes the food down toward the pylorus, mixing food with acid and digestive enzymes. As large food particles are digested to the more uniform texture of chyme, each contractile wave squirts a small amount of chyme through the pylorus into the duodenum. Enhanced gastric motility during a meal is primarily under neural control and is stimulated by distension of the stomach.

Gastric Secretions Protect and Digest

The lumen of the stomach is lined with mucus-producing epithelium punctuated by the openings of *gastric pits*. The pits lead to **gastric glands** deep within the mucosal layer (see Fig. 21.1e). Multiple cell types within the glands produce gastric acid (HCl), enzymes, hormones, and paracrine molecules. The various secretions of gastric mucosa cells, their stimuli for release, and their functions are summarized in **FIGURE 21.9** and described next.

Gastrin Secretion **G cells,** found deep in the gastric glands, secrete the hormone **gastrin** into the blood. In short reflexes, gastrin release is stimulated by the presence of amino acids and peptides in the stomach and by distension of the stomach. Coffee (even if decaffeinated) also stimulates gastrin release—one reason people with excess acid secretion syndromes are advised to avoid coffee.

Gastrin release is also triggered by neural reflexes. Short reflexes are mediated by an ENS neurotransmitter called **gastrin-releasing peptide** (GRP). In cephalic reflexes, parasympathetic neurons from the vagus nerve stimulate G cells to release gastrin into the blood.

Gastrin's primary action is to promote acid release. It does this directly by acting on parietal cells and indirectly by stimulating histamine release.

Acid Secretion **Parietal cells** deep in the gastric glands secrete **gastric acid** (HCl) into the lumen of the stomach. Acid secretion in the stomach averages 1–3 liters per day and can create a luminal pH as low as 1. The cytoplasmic pH of the parietal cells is about 7.2, which means the cells are pumping H^+ against a gradient that can be 1.5 million times more concentrated in the lumen.

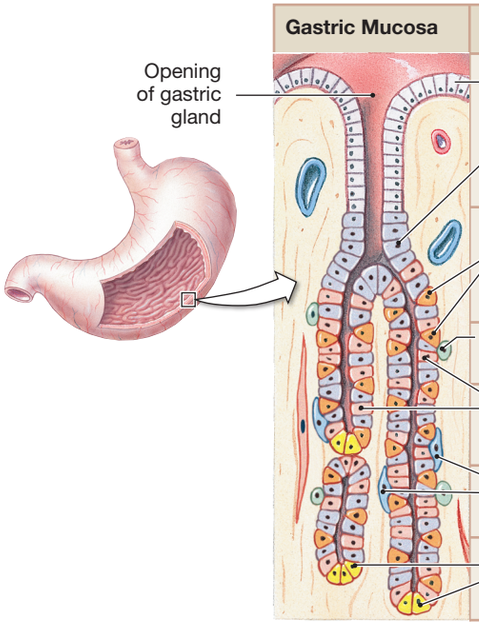
Gastric acid has multiple functions:

- Acid in the stomach lumen causes release and activation of pepsin, an enzyme that digests proteins.
- Acid triggers somatostatin release from D cells. Somatostatin is discussed later in the section on paracrine signals.
- HCl *denatures* proteins by breaking disulfide and hydrogen bonds that hold the protein in its tertiary structure [p. 32]. Unfolding protein chains make the peptide bonds between amino acids more accessible to digestion by pepsin.
- Gastric acid helps kill bacteria and other ingested microorganisms.
- Acid inactivates salivary amylase, stopping carbohydrate digestion that began in the mouth.

The parietal cell pathway for acid secretion is depicted in Figure 21.9c. The process begins when H^+ from water inside the parietal cell is pumped into the stomach lumen by an

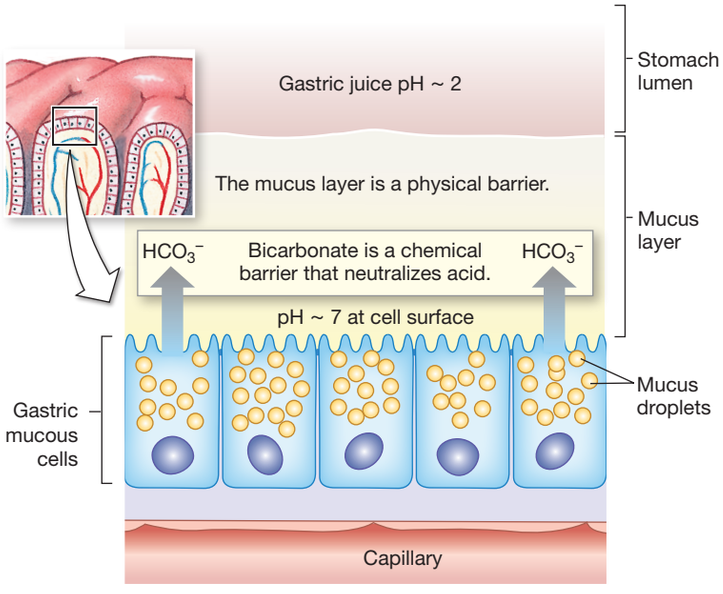
Gastric Secretions

(a) Secretory Cells of the Gastric Mucosa

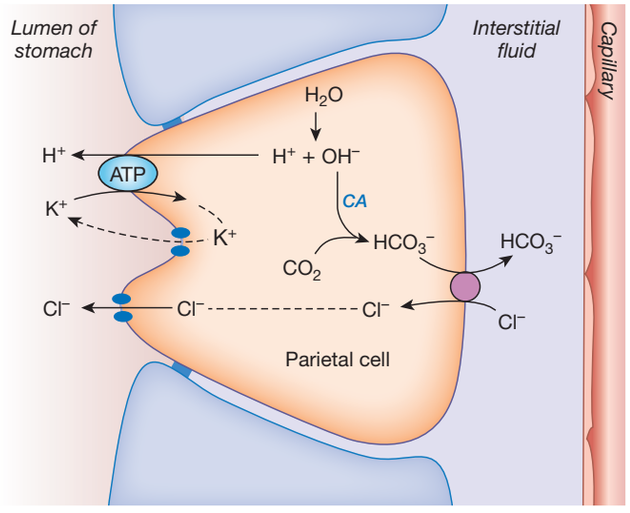


Gastric Mucosa	Cell Types	Substance Secreted	Function of Secretion	Stimulus for Release
	Mucous surface cell	Mucus	Physical barrier between lumen and epithelium	Tonic secretion; irritation of mucosa
	Mucous neck cell	Bicarbonate	Buffers gastric acid to prevent damage to epithelium	Secreted with mucus
	Parietal cells	Gastric acid (HCl)	Activates pepsin; kills bacteria	Acetylcholine, gastrin, histamine
		Intrinsic factor	Complexes with vitamin B_{12} to permit absorption	
	Enterochromaffin-like cell	Histamine	Stimulates gastric acid secretion	Acetylcholine, gastrin
	Chief cells	Pepsin(ogen)	Digests proteins	Acetylcholine, acid secretion
		Gastric lipase	Digests fats	
	D cells	Somatostatin	Inhibits gastric acid secretion	Acid in the stomach
	G cells	Gastrin	Stimulates gastric acid secretion	Acetylcholine, peptides, and amino acids

(b) Mucus-Bicarbonate Barrier



(c) Acid Secretion in the Stomach



H^+-K^+-ATPase in exchange for K^+ entering the cell. Cl^- then follows the electrical gradient created by H^+ by moving through open chloride channels. The net result is secretion of HCl by the cell.

By learning the cellular mechanism of parietal cell acid secretion, scientists were able to develop a new class of drugs to treat oversecretion of gastric acid. These drugs, known as *proton pump inhibitors (PPIs),* block activity of the H^+-K^+-ATPase. Generic versions of some PPIs (omeprazole, for example) are available over the counter in the United States.

While acid is being secreted into the lumen, bicarbonate made from CO_2 and the OH^- from water is absorbed into the blood. The buffering action of HCO_3^- makes blood leaving the stomach less acidic, creating an *alkaline tide* that can be measured as a meal is being digested.

RUNNING **PROBLEM**

Brooke, who had always been healthy, was baffled. How could she have contracted cholera? But after discussing the methods of transmission with her healthcare providers, she realized that she hadn't been as careful about consuming only bottled water as she should have been. One of the doctors noticed that Brooke's medical history form listed Nexium® (esomeprazole) among her current medications. "You know, taking Nexium might have also contributed to your contracting cholera."

Q3: *Esomeprazole is a proton pump inhibitor (PPI). For what symptom or condition might Brooke have been taking this drug?*

Q4: *Why might taking a protein pump inhibitor like esomeprazole have increased Brooke's chances of contracting cholera?*

655 659 672 675 682 688

Enzyme Secretion The stomach produces two enzymes: pepsin and a gastric lipase. **Pepsin** carries out the initial digestion of proteins. It is particularly effective on collagen and therefore plays an important role in digesting meat.

Pepsin is secreted as the inactive enzyme *pepsinogen* by **chief cells** in the gastric glands. Acid stimulates pepsinogen release from chief cells through a short reflex mediated in the ENS (**FIG. 21.10**). Once in the stomach lumen, pepsinogen is cleaved to active pepsin by the action of H^+, and protein digestion begins.

Gastric lipase is co-secreted with pepsin. Lipases are enzymes that break down triglycerides. However, less than one-third of fat digestion takes place in the stomach.

Paracrine Secretions Paracrine secretions from the gastric mucosa include histamine, somatostatin, and intrinsic factor. **Histamine** is a paracrine signal secreted by **enterochromaffin-like cells (ECL cells)** in response to gastrin or acetylcholine stimulation. Histamine diffuses to its target, the parietal cells, and stimulates acid secretion by combining with *H_2 receptors* on parietal cells (Fig. 21.10). *H_2 receptor antagonists* (cimetidine and ranitidine, for example) that block histamine action are a second class of drugs used to treat acid hypersecretion.

Intrinsic factor is a protein secreted by the same gastric parietal cells that secrete acid. In the lumen of the stomach intrinsic factor complexes with vitamin B_{12}, a step that is needed for the vitamin's absorption in the intestine.

Somatostatin (SS), also known as hypothalamic growth hormone-inhibiting hormone, is secreted by **D cells** in the stomach. Somatostatin is the primary negative feedback signal for gastric phase secretion. It shuts down acid secretion directly and indirectly by decreasing gastrin and histamine secretion. Somatostatin also inhibits pepsinogen secretion (Fig. 21.10).

The Stomach Balances Digestion and Defense

Under normal conditions, the gastric mucosa protects itself from autodigestion by acid and enzymes with a mucus-bicarbonate barrier. **Mucous cells** on the luminal surface and in the neck of gastric glands secrete both substances. The mucus forms a physical barrier, and the bicarbonate creates a chemical buffer barrier underlying the mucus (Fig. 21.9b).

Researchers using microelectrodes have shown that the bicarbonate layer just above the cell surface in the stomach has a pH that is close to 7, even when the pH in the lumen is highly acidic at pH 2. Mucus secretion is increased when the stomach is irritated, such as by the ingestion of aspirin (acetylsalicylic acid) or alcohol.

Even the protective mucus-bicarbonate barrier can fail at times. In *Zollinger-Ellison syndrome,* patients secrete excessive levels of gastrin, usually from gastrin-secreting tumors in the pancreas. As a result, hyperacidity in the stomach overwhelms the normal protective mechanisms and causes a peptic ulcer. In peptic ulcers, acid and pepsin destroy the mucosa, creating holes that extend into the submucosa and muscularis of the stomach and duodenum. *Acid reflux* into the esophagus can erode the mucosal layer there as well.

Excess acid secretion is an uncommon cause of peptic ulcers. By far the most common causes are nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, and *Helicobacter pylori,* a bacterium that creates inflammation of the gastric mucosa.

For many years the primary therapy for excess acid secretion, or *dyspepsia,* was the ingestion of *antacids,* agents that neutralize acid in the gastric lumen. But as molecular biologists discovered the mechanism for acid secretion by parietal cells, the potential for new therapies became obvious. Today, we have two classes of drugs to fight hyperacidity: the H_2 receptor antagonists and proton pump inhibitors that block the H^+-K^+-ATPase.

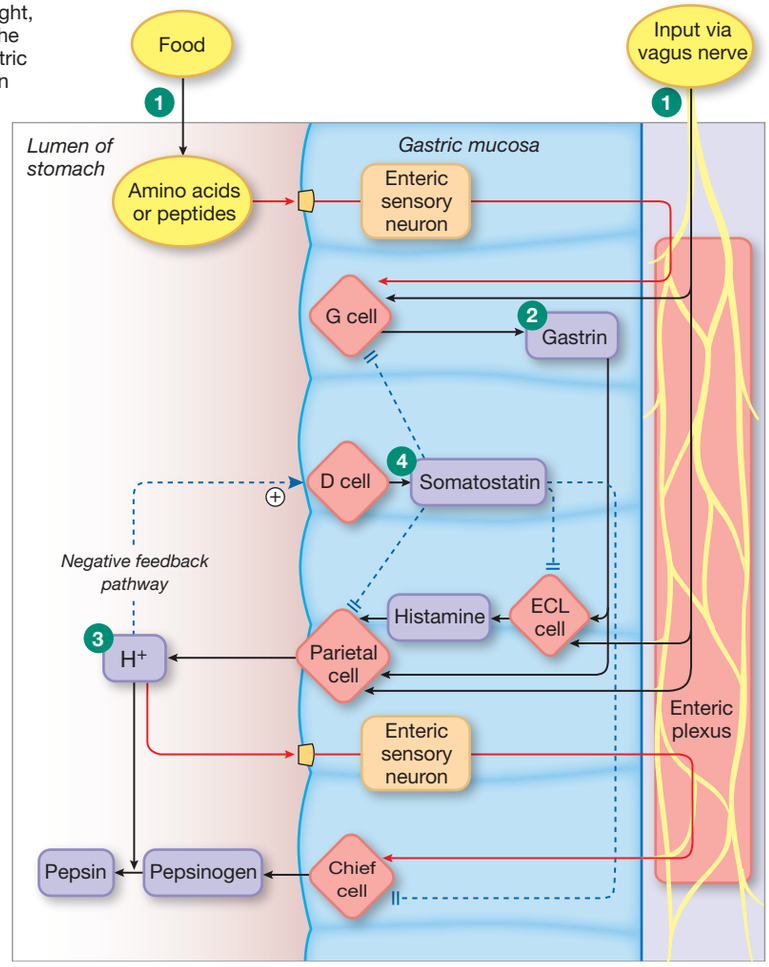
INTEGRATED FUNCTION: THE INTESTINAL PHASE

Once chyme passes into the small intestine, the **intestinal phase** of digestion begins. Chyme entering the small intestine has undergone relatively little chemical digestion, so its entry must be controlled to avoid overwhelming the small intestine. Motility in the small intestine is also controlled. Intestinal contents are slowly propelled forward by a combination of segmental and peristaltic contractions. These actions mix chyme with enzymes and they expose digested nutrients to the mucosal epithelium for absorption. Forward movement of chyme through the intestine must be slow enough to allow digestion and absorption to go to completion. Parasympathetic innervation and the GI hormones gastrin and CCK promote intestinal motility; sympathetic innervation inhibits it.

About 5.5 liters of food, fluid, and secretions enter the small intestine each day, and about 3.5 liters of hepatic, pancreatic,

FIG. 21.10 Integration of cephalic and gastric phase secretion

The cephalic phase is initiated by the sight, smell, sound, or thought of food or by the presence of food in the mouth. The gastric phase is initiated by the arrival of food in the stomach.



1. Food or cephalic reflexes initiate gastric secretion of gastrin, histamine, and acid.
2. Gastrin stimulates acid secretion by direct action on parietal cells or indirectly through histamine.
3. Acid stimulates short reflex secretion of pepsinogen.
4. Somatostatin release by H^+ is the negative feedback signal that modulates acid and pepsin release.

FIGURE QUESTIONS

1. Is the autonomic vagal input sympathetic or parasympathetic?
2. What are the neurotransmitter and receptor for this input?

and intestinal secretions are added there, making a total input of 9 liters into the lumen (see Fig. 21.3). All but about 1.5 liters of this volume is absorbed in the small intestine, mostly in the duodenum and jejunum.

The anatomy of the small intestine facilitates secretion, digestion, and absorption by maximizing surface area (**FIGS. 21.11** and 21.1f). At the macroscopic level, the surface of the lumen is sculpted into fingerlike villi and deep crypts. Most absorption takes place along the villi while fluid and hormone secretion and cell renewal from stem cells occurs in the crypts. On a microscopic level the apical surface of the enterocytes is modified into microvilli whose surfaces are covered with membrane-bound enzymes and a *glycocalyx* coat [p. 64]. The surface of the intestinal epithelium is called the **brush border** from the bristle-like appearance of the microvilli.

Most nutrients absorbed across the intestinal epithelium move into capillaries in the villi for distribution through the circulatory system. The exception is digested fats, most of which pass into lacteals of the lymphatic system. Venous blood from the digestive tract does not go directly back to the heart. Instead, it passes into the *hepatic portal system* [p. 439]. This specialized region of the circulation has two sets of capillary beds: one that picks up absorbed nutrients at the intestine, and another that delivers the nutrients directly to the liver (**FIG. 21.12**).

The delivery of absorbed materials directly to the liver underscores the importance of that organ as a biological filter. Hepatocytes contain a variety of enzymes, such as the *cytochrome P450* isozymes, that metabolize drugs and xenobiotics and clear them from the bloodstream before they reach the systemic circulation. Hepatic clearance is one reason a drug administered orally must often be given in higher doses than the same drug administered by IV infusion.

Intestinal Secretions Promote Digestion

Each day, the liver, pancreas, and intestine produce more than 3 liters of secretions whose contents are necessary for completing the digestion of ingested nutrients. The added secretions include

FIG. 21.11 The villus and a crypt in the small intestine

Villi and crypts increase the effective surface area of the small intestine. Stem cells in the crypts produce new epithelial cells to replace those that die or are damaged. Most absorption occurs along the villi. Most fluid secretion occurs in the crypts.

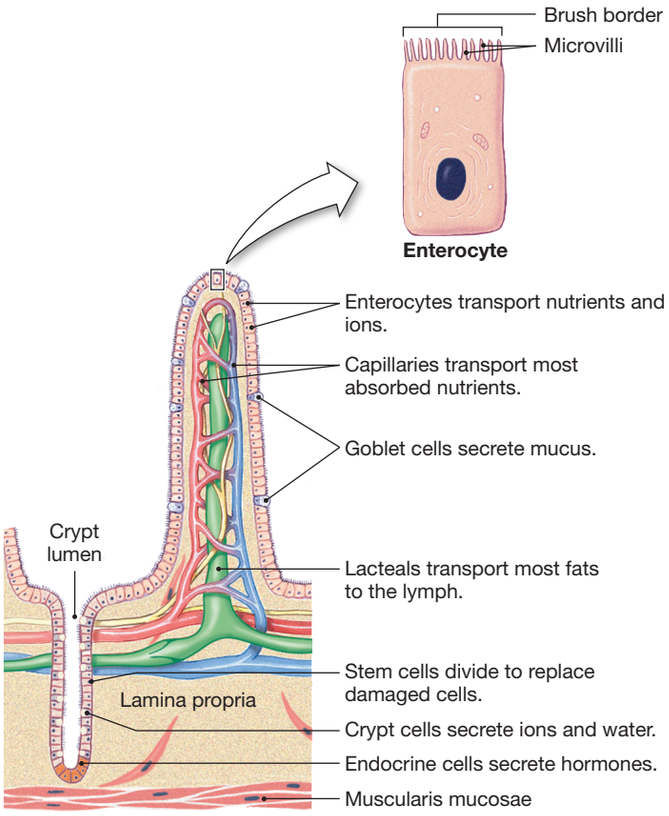
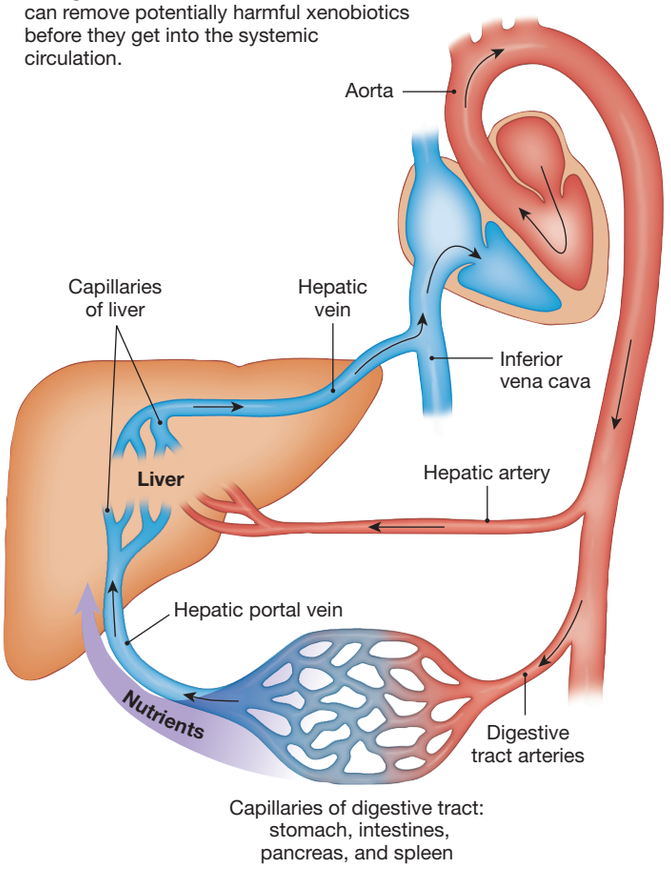


FIG. 21.12 The hepatic portal system

Most nutrients absorbed by the intestine pass through the liver, which serves as a filter that can remove potentially harmful xenobiotics before they get into the systemic circulation.



digestive enzymes, bile, bicarbonate, mucus, and an isotonic NaCl solution.

1. *Digestive enzymes* are produced by the intestinal epithelium and the exocrine pancreas. Intestinal brush border enzymes are anchored to the luminal cell membranes and are not swept out of the small intestine as chyme is propelled forward. The control pathways for enzyme release vary but include a variety of neural, hormonal, and paracrine signals. Usually, stimulation of parasympathetic neurons in the vagus nerve enhances enzyme secretion.
2. *Bile* made in the liver and released from the gall bladder is a nonenzymatic solution that facilitates the digestion of fats.
3. *Bicarbonate secretion* into the small intestine neutralizes the highly acidic chyme that enters from the stomach. Most bicarbonate comes from the pancreas and is released in response to neural stimuli and secretin.
4. *Mucus* from intestinal goblet cells protects the epithelium and lubricates the gut's contents.
5. An *isotonic NaCl solution* mixes with mucus to help lubricate the contents of the gut.

Isotonic NaCl Secretion Crypt cells in the small intestine and colon secrete an isotonic NaCl solution in a process similar to the initial step of salivation (**FIG. 21.13**). Chloride from the ECF enters cells via NKCC transporters, then exits into the lumen via an apical gated Cl^- channel known as the **cystic fibrosis transmembrane conductance regulator,** or **CFTR channel.** Movement of negatively charged Cl^- into the lumen draws Na^+ down the electrical gradient through leaky cell junctions. Water follows Na^+ along the osmotic gradient created by redistribution of NaCl. The result is secretion of isotonic saline solution.

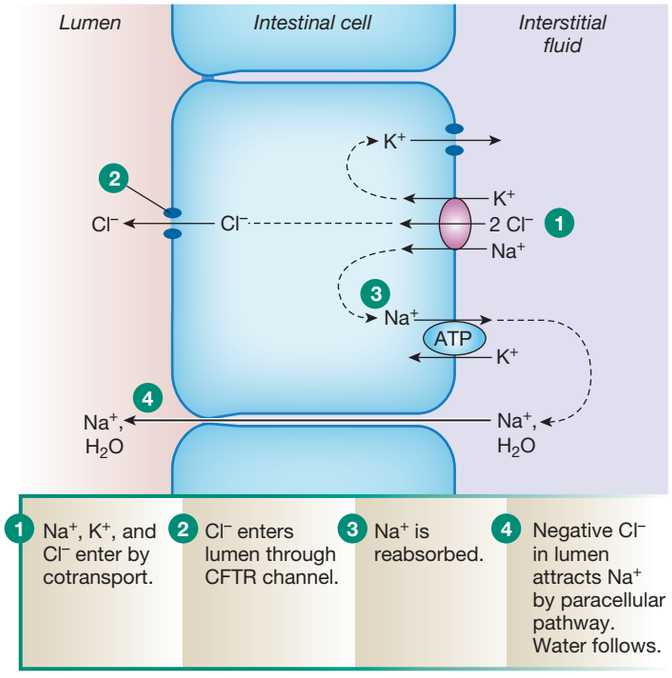
The Pancreas Secretes Enzymes and Bicarbonate

The pancreas is an organ that contains both types of secretory epithelium: endocrine and exocrine [p. 79]. Endocrine secretions come from clusters of cells called *islets* and include the hormones insulin and glucagon (**FIG. 21.14**). Exocrine secretions include digestive enzymes and a watery solution of sodium bicarbonate, $NaHCO_3$.

The exocrine portion of the pancreas consists of lobules called *acini,* similar to those of the salivary glands. Ducts from the acini

FIG. 21.13 Isotonic NaCl secretion

Intestinal and colonic crypt cells and salivary gland acini secrete isotonic NaCl solutions.



empty into the duodenum (Fig. 21.14a). The acinar cells secrete digestive enzymes, and the duct cells secrete the $NaHCO_3$ solution.

Enzyme Secretion Most pancreatic enzymes are secreted as zymogens that must be activated upon arrival in the intestine. This activation process is a cascade that begins when brush border **enteropeptidase** (previously called *enterokinase*) converts inactive trypsinogen to active trypsin (Fig. 21.14b). Trypsin then converts the other pancreatic zymogens to their active forms.

The signals for pancreatic enzyme release include distension of the small intestine, the presence of food in the intestine, neural signals, and the GI hormone CCK. Pancreatic enzymes enter the intestine in a watery fluid that also contains bicarbonate.

Bicarbonate Secretion Bicarbonate secretion into the duodenum neutralizes acid entering from the stomach. A small amount of bicarbonate is secreted by duodenal cells, but most comes from the pancreas.

Bicarbonate production requires high levels of the enzyme *carbonic anhydrase,* levels similar to those found in renal tubule cells and red blood cells [pp. 577, 646]. Bicarbonate produced from CO_2 and water is secreted by an apical Cl^--HCO_3^- exchanger (Fig. 21.14c). Hydrogen ions produced along with bicarbonate leave the cell on basolateral Na^+-H^+ exchangers. The H^+ thus reabsorbed into the intestinal circulation helps balance HCO_3^- put into the blood when parietal cells secrete H^+ into the stomach (see Fig. 21.9c).

The chloride for bicarbonate exchange enters the cell on a basolateral NKCC cotransporter and leaves via an apical CFTR channel. Luminal Cl^- then re-enters the cell in exchange for HCO_3^- entering the lumen. Defects in CFTR channel structure or function cause the disease *cystic fibrosis,* and disruption of pancreatic secretion is one hallmark of cystic fibrosis.

In cystic fibrosis, an inherited mutation causes the CFTR channel protein to be defective or absent. As a result, secretion of Cl^- and fluid ceases but goblet cells continue to secrete mucus, resulting in thickened mucus. In the digestive system, the thick mucus clogs small pancreatic ducts and prevents digestive enzyme secretion into the intestine. In airways of the respiratory system, where the CFTR channel is also found, failure to secrete fluid clogs the mucociliary escalator [Fig. 17.5c, p. 541] with thick mucus, leading to recurrent lung infections.

In both the pancreas and intestinal crypts, sodium and water secretion is a passive process, driven by electrochemical and osmotic gradients. The movement of negative ions from the ECF to the lumen creates a lumen-negative electrical gradient that attracts Na^+. Sodium moves down its electrochemical gradient through leaky junctions between the cells. The transfer of Na^+ and HCO_3^- from ECF into the lumen creates an osmotic gradient, and water follows by osmosis. The net result is secretion of a watery sodium bicarbonate solution.

The Liver Secretes Bile

Bile is a nonenzymatic solution secreted from **hepatocytes,** or liver cells (see *Focus On: The Liver,* **FIG. 21.15**). The key components of bile are (1) **bile salts,** which facilitate enzymatic fat digestion, (2) *bile pigments,* such as bilirubin, which are the waste products of hemoglobin degradation, and (3) *cholesterol,* which is excreted in the feces. Drugs and other xenobiotics are cleared from the blood by hepatic processing and are also excreted in bile. Bile salts, which act as detergents to make fats soluble during digestion, are made from steroid **bile acids** combined with amino acids.

RUNNING PROBLEM

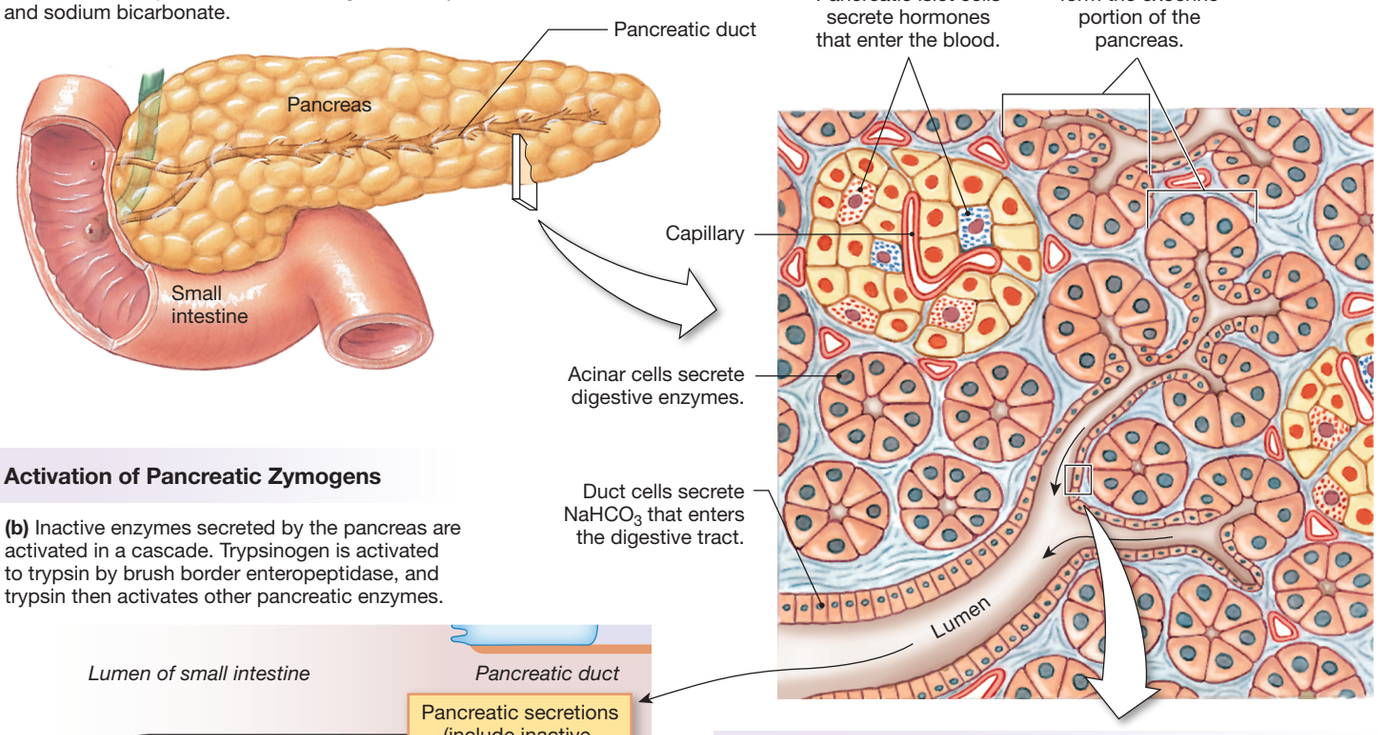
A hallmark of *Vibrio cholerae* infection is profuse, dilute diarrhea sometimes said to resemble "rice water." The toxin secreted by *Vibrio cholerae* is a protein complex with six subunits. The toxin binds to intestinal cells, and the A subunit is taken into the enterocytes by endocytosis. Once inside the enterocyte, the toxin turns on adenylyl cyclase, which then produces cAMP continuously. Because the CFTR channel of the enterocyte is a cAMP-gated channel, the effect of cholera toxin is to open the CFTR channels and keep them open.

Q5: *Why would continuously open enterocyte CFTR channels cause secretory diarrhea and dehydration in humans?*

The Pancreas

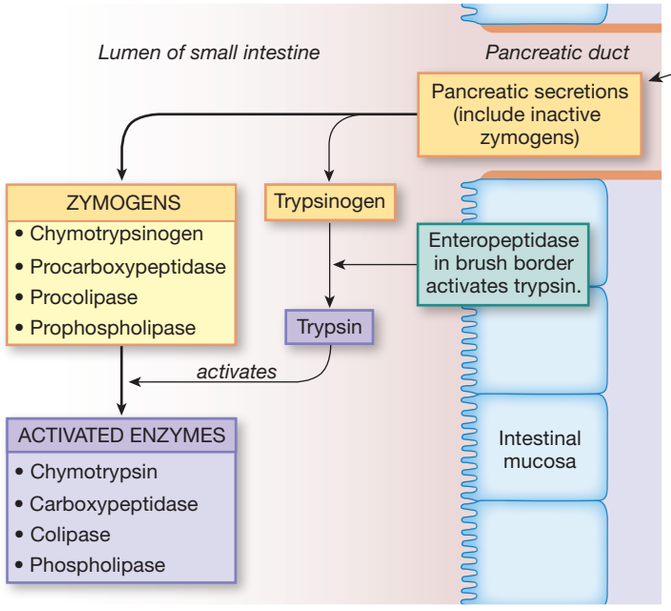
Anatomy of the Exocrine and Endocrine Pancreas

(a) The exocrine pancreas secretes digestive enzymes and sodium bicarbonate.



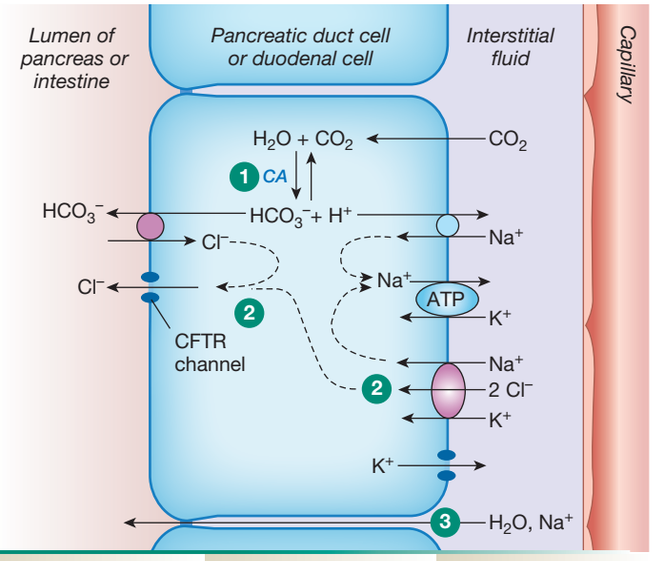
Activation of Pancreatic Zymogens

(b) Inactive enzymes secreted by the pancreas are activated in a cascade. Trypsinogen is activated to trypsin by brush border enteropeptidase, and trypsin then activates other pancreatic enzymes.



Bicarbonate Secretion

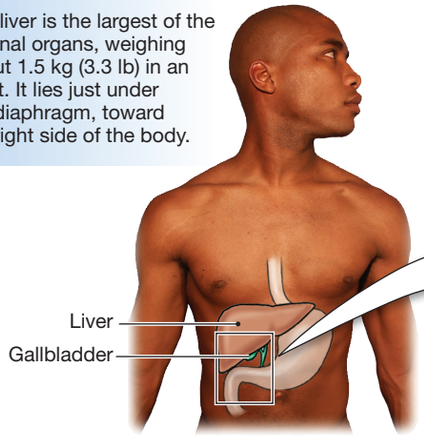
(c) Bicarbonate secretion in the pancreas and duodenum



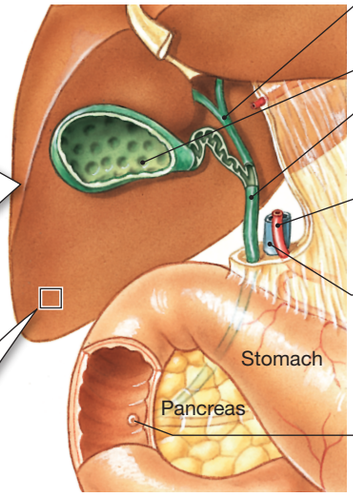
1. Cells that produce bicarbonate have high concentrations of carbonic anhydrase (CA).
2. Chloride enters cells by indirect active transport and leaves the apical side through a CFTR channel. Cl^- then reenters the cell in exchange for HCO_3^-.
3. Leaky junctions allow paracellular movement of ions and water. Negative ions in the lumen attract Na^+ by the paracellular pathway. Water follows.

The Liver

(a) The liver is the largest of the internal organs, weighing about 1.5 kg (3.3 lb) in an adult. It lies just under the diaphragm, toward the right side of the body.



(b) Gallbladder and bile ducts



Common hepatic duct takes bile made in the liver to the gallbladder for storage.

Gallbladder

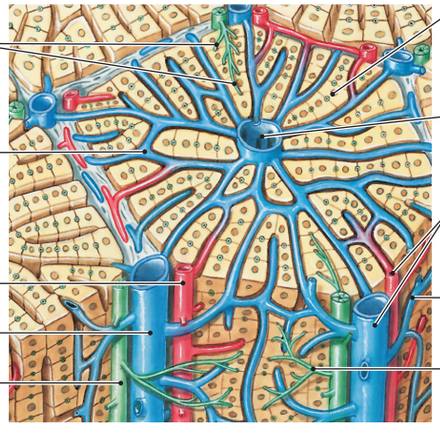
Common bile duct takes bile from the gallbladder to the lumen of the small intestine.

Hepatic artery brings oxygenated blood containing metabolites from peripheral tissues to the liver.

Hepatic portal vein blood is rich in absorbed nutrients from the gastrointestinal tract and contains hemoglobin breakdown products from the spleen. Blood leaves the liver in the hepatic vein (not shown).

Sphincter of Oddi controls release of bile and pancreatic secretions into the duodenum.

(c) The hepatocytes of the liver are organized into irregular hexagonal units called **lobules.**



Hepatocytes are liver cells. About 70% of the surface area of each hepatocyte faces the sinusoids, maximizing the exchange between the blood and the cells.

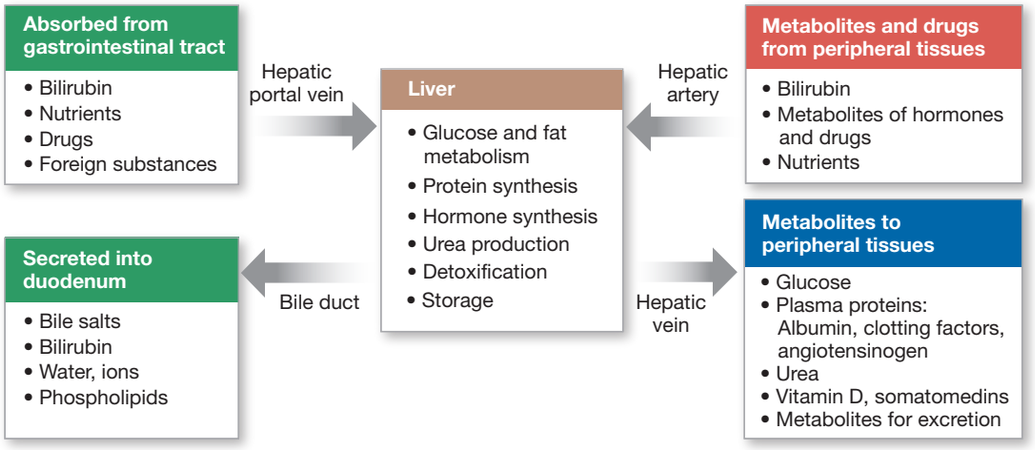
Each lobule is centered around a central vein that drains blood into the hepatic vein.

Along its periphery, a lobule is associated with branches of the hepatic portal vein and hepatic artery.

These vessels branch among the hepatocytes, forming **sinusoids** into which the blood flows.

The **bile canaliculi** are small channels into which bile is secreted. The canaliculi coalesce into bile ductules that run through the liver alongside the portal veins.

(d) Blood entering the liver brings nutrients and foreign substances from the digestive tract, bilirubin from hemoglobin breakdown, and metabolites from peripheral tissues of the body. In turn, the liver excretes some of these in the bile and stores or metabolizes others. Some of the liver's products are wastes to be excreted by the kidney; others are essential nutrients, such as glucose. In addition, the liver synthesizes an assortment of plasma proteins.



Bile secreted by hepatocytes travels in hepatic ducts to the **gallbladder,** which stores and concentrates the bile solution. During a meal that includes fats, contraction of the gallbladder sends bile into the duodenum through the **common bile duct.** The gallbladder is an organ that is not essential for normal digestion, and if the duct becomes blocked by hard deposits known as gallstones, the gallbladder can be removed without creating long-term problems.

Bile salts are not altered during fat digestion. When they reach the terminal section of the small intestine (the ileum), they encounter cells that reabsorb them and send them back into the circulation. From there, bile salts return to the liver, where the hepatocytes take them back up and re-secrete them. This recirculation of bile salts is essential to fat digestion because the body's pool of bile salts must cycle from two to five times for each meal. Bilirubin and other wastes secreted in bile cannot be reabsorbed and pass into the large intestine for excretion.

Most Digestion Occurs in the Small Intestine

The intestinal, pancreatic, and hepatic secretion of enzymes and bile is essential for normal digestive function. Although a significant amount of mechanical digestion takes place in the mouth and stomach, chemical digestion of food there is limited to a small amount of starch breakdown and incomplete protein digestion in the stomach. When chyme enters the small intestine, protein digestion stops when pepsin is inactivated at the higher intestinal pH. Pancreatic and brush border enzymes then finish digestion of peptides, carbohydrates, and fats into smaller molecules that can be absorbed.

Bile Salts Facilitate Fat Digestion

Fats and related molecules in the Western diet include triglycerides, cholesterol, phospholipids, long-chain fatty acids, and the fat-soluble vitamins [Fig. 2.1, p. 30]. Nearly 90% of our fat calories come from triglycerides because they are the primary form of lipid in both plants and animals.

Fat digestion is complicated by the fact that most lipids are not particularly water soluble. As a result, the aqueous chyme leaving the stomach contains a coarse emulsion of large fat droplets, which have less surface area than smaller particles. To increase the surface area available for enzymatic fat digestion, the liver secretes bile salts into the small intestine (**FIG. 21.16a**). Bile salts help break down the coarse emulsion into smaller, more stable particles.

Bile salts, like phospholipids of cell membranes, are *amphipathic* {*amphi-,* on both sides + *pathos,* experience}, meaning that they have both a hydrophobic region and a hydrophilic region. The hydrophobic regions of bile salts associate with the surface of lipid droplets while the polar side chains interact with water, creating a stable emulsion of small, water-soluble fat droplets (Fig. 21.16a). You can see a similar emulsion when you shake a bottle of salad dressing to combine the oil and aqueous layers.

Enzymatic fat digestion is carried out by **lipases,** enzymes that remove two fatty acids from each triglyceride molecule. The result is one monoglyceride and two free fatty acids (Fig. 21.16c). The bile salt coating of the intestinal emulsion complicates digestion, however, because lipase is unable to penetrate the bile salts. For this reason, fat digestion also requires **colipase,** a protein cofactor secreted by the pancreas. Colipase displaces some bile salts, allowing lipase access to fats inside the bile salt coating.

Phospholipids are digested by pancreatic *phospholipase.* Free cholesterol is not digested and is absorbed intact.

As enzymatic and mechanical digestion proceed, fatty acids, bile salts, mono- and diglycerides, phospholipids, and cholesterol coalesce to form small disk-shaped **micelles** (Fig. 21.16b) [p. 63]. Micelles then enter the unstirred aqueous layer at the edge of the brush border.

Fat Absorption Lipophilic fats such as fatty acids and monoglycerides are absorbed primarily by simple diffusion. They move out of their micelles and diffuse across the enterocyte membrane into the cells (Fig. 21.16d). Initially scientists believed that cholesterol also diffused across the enterocyte membrane, but the discovery of a drug called *ezetimibe* that inhibits cholesterol absorption suggested that transport proteins were involved. Experiments now indicate that some cholesterol is transported across the brush border membrane on specific, energy-dependent membrane transporters, including one named *NPC1L1,* the protein that is inhibited by ezetimibe.

Once monoglycerides and fatty acids are inside the enterocytes, they move to the smooth endoplasmic reticulum, where they recombine into triglycerides (Fig. 21.16d). The triglycerides then join cholesterol and proteins to form large droplets called **chylomicrons.** Because of their size, chylomicrons must be packaged into secretory vesicles by the Golgi. The chylomicrons then leave the cell by exocytosis.

The large size of chylomicrons also prevents them from crossing the basement membrane of capillaries (Fig. 21.16d). Instead, chylomicrons are absorbed into *lacteals,* the lymph vessels of the villi. Chylomicrons pass through the lymphatic system and finally enter the venous blood just before it flows into the right side of the heart [p. 499].

Some shorter fatty acids (10 or fewer carbons) are not assembled into chylomicrons. These fatty acids can therefore cross the capillary basement membrane and go directly into the blood.

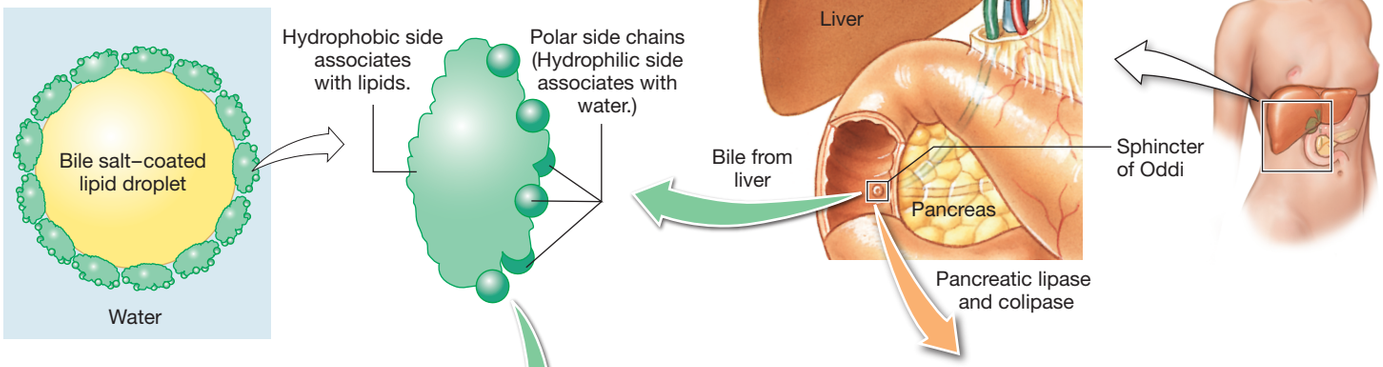
CONCEPT CHECK

12. Do bile salts digest triglycerides into monoglycerides and free fatty acids?
13. Bile acids are reabsorbed in the distal intestine by an apical sodium-dependent bile acid transporter (ASBT) and a basolateral organic anion transporter (OAT). Draw one enterocyte. Label the lumen, ECF, and basolateral and apical sides. Diagram bile acid reabsorption as described.
14. Explain how pH can be used to predict the location where a particular digestive enzyme might be most active.

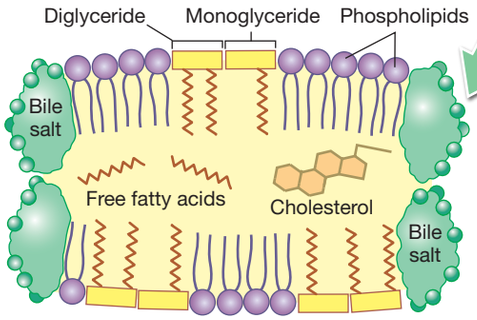
Digestion and Absorption: Fats

Most lipids are hydrophobic and must be emulsified to facilitate digestion in the aqueous environment of the intestine.

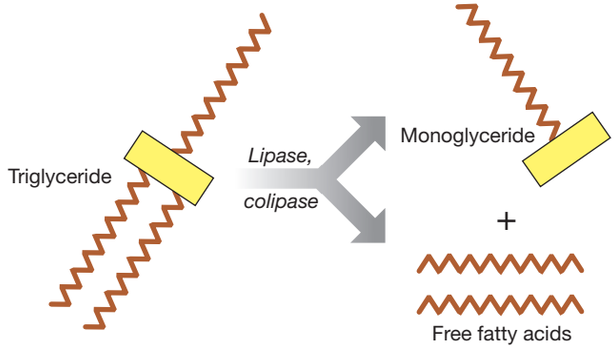
(a) Bile salts coat lipids to make emulsions.



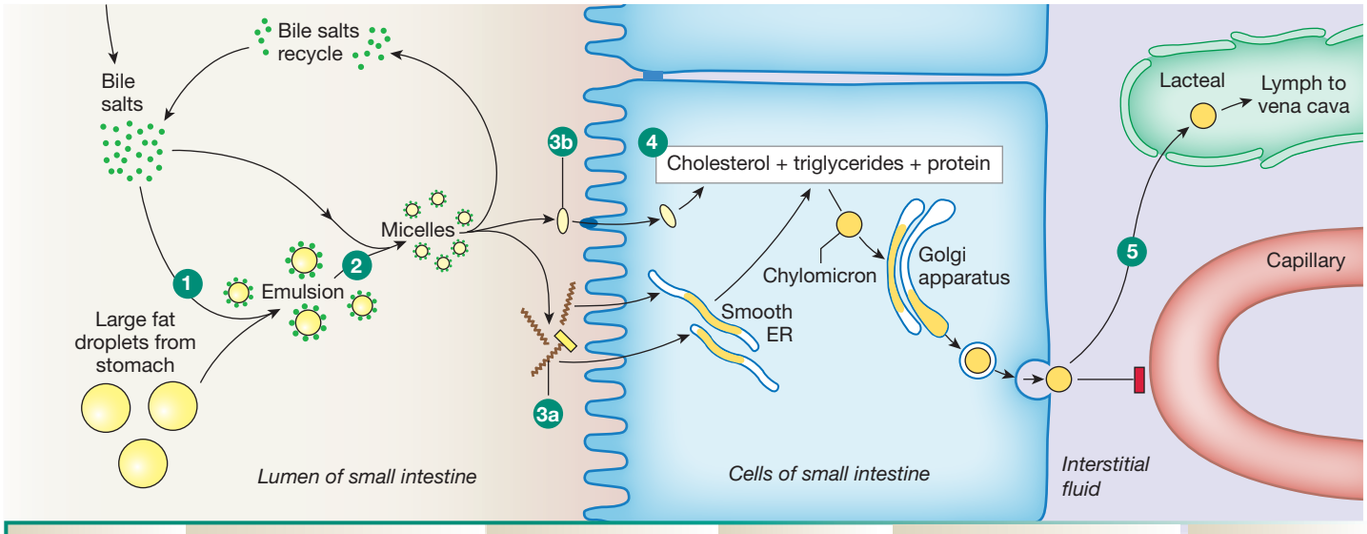
(b) Micelles are small disks with bile salts, phospholipids, fatty acids, cholesterol, and mono- and diglycerides.



(c) Lipase and colipase digest triglycerides.



(d) Fat digestion and absorption

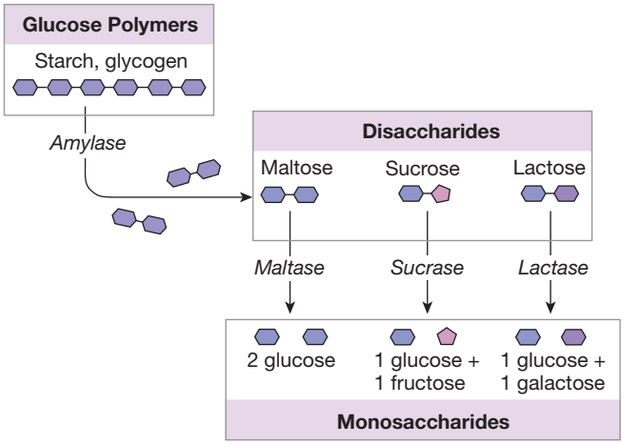


1. Bile salts from liver coat fat droplets.
2. Pancreatic lipase and colipase break down fats into monoglycerides and fatty acids stored in micelles.
3a. Monoglycerides and fatty acids move out of micelles and enter cells by diffusion.
3b. Cholesterol is transported into cells.
4. Absorbed fats combine with cholesterol and proteins in the intestinal cells to form chylomicrons.
5. Chylomicrons are removed by the lymphatic system.

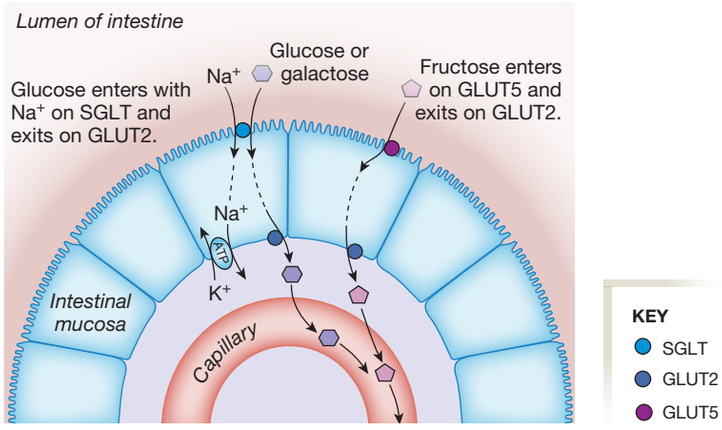
Digestion and Absorption of Carbohydrates

Most carbohydrates in our diets are disaccharides and complex carbohydrates. Cellulose is not digestible. All other carbohydrates must be digested to monosaccharides before they can be absorbed.

(a) Carbohydrates break down into monosaccharides.



(b) Carbohydrate absorption in the small intestine



Carbohydrates Are Absorbed as Monosaccharides

About half the calories the average American ingests are in the form of carbohydrates, mainly *starch* and *sucrose* (table sugar). Other dietary carbohydrates include the glucose polymers *glycogen* and *cellulose*, disaccharides such as *lactose* (milk sugar) and *maltose*, and the monosaccharides *glucose* and *fructose* [Fig. 2.2, p. 31]. The enzyme *amylase* breaks long glucose polymers into smaller glucose chains and into the disaccharide maltose (**FIG. 21.17a**).

Starch digestion starts in the mouth with salivary amylase but that enzyme is denatured in the acidic stomach. Pancreatic amylase then resumes digestion of starch into maltose. Maltose and other disaccharides are broken down by intestinal brush-border enzymes known as **disaccharidases** (maltase, sucrase, and lactase). The absorbable end products of carbohydrate digestion are glucose, galactose, and fructose.

Because intestinal carbohydrate absorption is restricted to monosaccharides, all larger carbohydrates must be digested if they are to be used by the body. The complex carbohydrates we can digest are starch and glycogen. We are unable to digest cellulose because we lack the necessary enzymes. As a result, the cellulose in plant matter becomes what is known as dietary *fiber* or *roughage* and is excreted undigested. Similarly, *sucralose* (Splenda®), the artificial sweetener made from sucrose, cannot be digested because chlorine atoms substituted for three hydroxyl groups block enzymatic digestion of the sugar derivative.

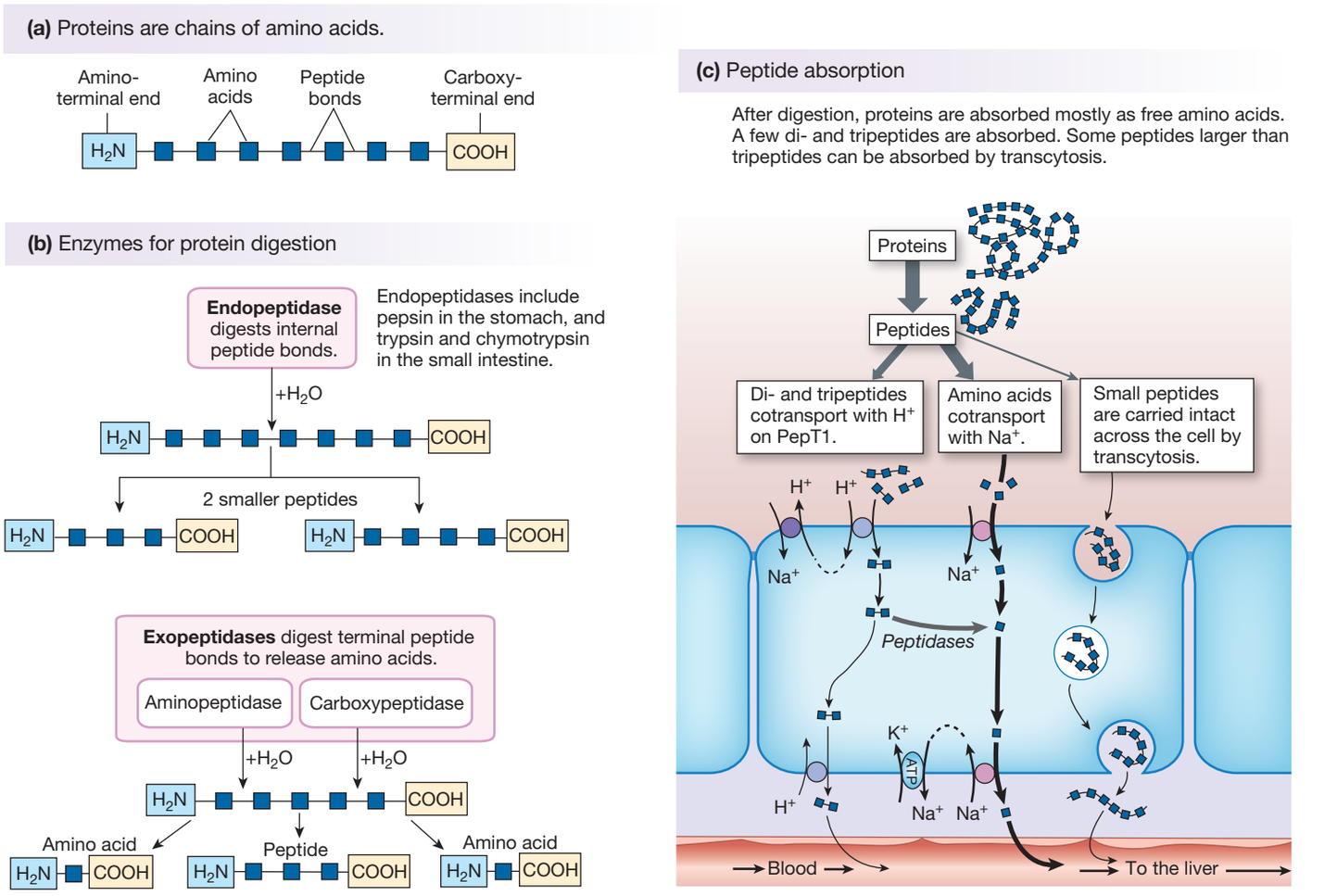
Carbohydrate Absorption Intestinal glucose and galactose absorption uses transporters identical to those found in the renal proximal tubule: the apical Na^+-glucose SGLT symporter and the basolateral GLUT2 transporter (Fig. 21.17b). These transporters move galactose as well as glucose. Fructose absorption, however, is not Na^+-dependent. Fructose moves across the apical membrane by facilitated diffusion on the GLUT5 transporter and across the basolateral membrane by GLUT2 [p. 144].

CLINICAL FOCUS

Lactose Intolerance

Lactose, or milk sugar, is a disaccharide composed of glucose and galactose. Ingested lactose must be digested before it can be absorbed, a task accomplished by the intestinal brush border enzyme *lactase*. Generally, lactase is found only in juvenile mammals, except in some humans of European descent. Those people inherit a dominant gene that allows them to produce lactase after childhood. Scientists believe the lactase gene provided a selective advantage to their ancestors, who developed a culture in which milk and milk products played an important role. In cultures in which dairy products are not part of the diet after weaning, most adults lack the gene and synthesize less intestinal lactase. Decreased lactase activity is associated with a condition known as *lactose intolerance*. If a person with lactose intolerance drinks milk or eats dairy products, diarrhea may result. In addition, bacteria in the large intestine ferment lactose to gas and organic acids, leading to bloating and flatulence. The simplest remedy is to remove milk products from the diet, although milk predigested with lactase is available.

Digestion and Absorption of Proteins



How are enterocytes able to keep intracellular glucose concentrations high so that facilitated diffusion moves glucose into the extracellular space? In most cells, glucose is the major metabolic substrate for aerobic respiration and is immediately phosphorylated when it enters the cell [p. 142]. However, the metabolism of enterocytes (and proximal tubule cells) apparently differs from that of most other cells. These transporting epithelial cells do not use glucose as their preferred energy source. Current studies indicate that these cells use the amino acid glutamine as their main source of energy, thus allowing absorbed glucose to pass unchanged into the bloodstream.

Proteins Are Digested into Small Peptides and Amino Acids

Unlike carbohydrates, which are ingested in forms ranging from simple to complex, most ingested proteins are polypeptides or larger [Fig. 2.3, p. 32]. Not all proteins are equally digestible by humans, however. Plant proteins are the least digestible. Among the most digestible is egg protein, 85–90% of which is in a form that can be digested and absorbed. Surprisingly, between 30% and 60% of the protein found in the intestinal lumen comes not from ingested food but from the sloughing of dead cells and from protein secretions such as enzymes and mucus.

The enzymes for protein digestion are classified into two broad groups: endopeptidases and exopeptidases (**FIG. 21.18b**). **Endopeptidases,** more commonly called **proteases,** attack peptide bonds in the interior of the amino acid chain and break a long peptide chain into smaller fragments. Proteases are secreted as inactive *proenzymes* (zymogens) from epithelial cells in the stomach, intestine, and pancreas. They are activated once they reach the GI tract lumen. Examples of proteases include **pepsin** secreted in the stomach, and **trypsin** and **chymotrypsin** secreted by the pancreas.

Exopeptidases release single amino acids from peptides by chopping them off the ends, one at a time. *Aminopeptidases* act on the amino-terminal end of the protein; *carboxypeptidases* act at the carboxy-terminal end. The most important digestive exopeptidases are two isozymes of carboxypeptidase secreted by the pancreas. Aminopeptidases play a lesser role in digestion.

CONCEPT CHECK **15.** What activates pepsinogen, trypsinogen, and chymotrypsinogen?

Protein Absorption The primary products of protein digestion are free amino acids, dipeptides, and tripeptides, all of which can be absorbed. Amino acid structure is so variable that multiple amino acid transport systems occur in the intestine. Most free amino acids are carried by Na^+-dependent cotransport proteins similar to those in the proximal tubule of the kidney (Fig. 21.18b). A few amino acid transporters are H^+-dependent.

Dipeptides and tripeptides are carried into enterocytes on the oligopeptide transporter *PepT1* that uses H^+-dependent cotransport (Fig. 21.18c). Once inside the epithelial cell, these *oligopeptides* {*oligos,* little} have two possible fates. Most are digested by cytoplasmic peptidases into individual amino acids, which are then transported across the basolateral membrane and into the circulation. Those oligopeptides that are not digested are transported intact across the basolateral membrane on an H^+-dependent exchanger. The transport system that moves oligopeptides also is responsible for intestinal uptake of certain drugs, including some antibiotics, angiotensin-converting enzyme inhibitors, and thrombin inhibitors.

Some Larger Peptides Can Be Absorbed Intact

Some peptides larger than three amino acids are absorbed by transcytosis [p. 152] after binding to membrane receptors on the luminal surface of the intestine. The discovery that ingested proteins can be absorbed as small peptides has implications in medicine because these peptides may act as *antigens,* substances that stimulate antibody formation and result in allergic reactions. Consequently, the intestinal absorption of peptides may be a significant factor in the development of food allergies and food intolerances.

In newborns, peptide absorption takes place primarily in intestinal crypt cells (Fig. 21.11). At birth, intestinal villi are very small, so the crypts are well exposed to the luminal contents. As the villi grow and the crypts have less access to chyme, the high peptide absorption rates present at birth decline steadily. If parents delay feeding the infant allergy-inducing peptides, the gut has a chance to mature, lessening the likelihood of antibody formation.

One of the most common antigens responsible for food allergies is gluten, a component of wheat. The incidence of childhood gluten allergies has decreased since the 1970s, when parents were cautioned not to feed infants gluten-based cereals until they were several months old.

In another medical application, pharmaceutical companies have developed indigestible peptide drugs that can be given orally instead of by injection. Probably the best-known example is *DDAVP* (1-deamino-8-D-arginine vasopressin), the synthetic analog of vasopressin. If the natural hormone vasopressin is ingested, it is digested rather than absorbed intact. By changing the structure of the hormone slightly, scientists created a synthetic peptide that has the same activity but is absorbed without being digested.

Nucleic Acids Are Digested into Bases and Monosaccharides

The nucleic acid polymers DNA and RNA are only a very small part of most diets. They are digested by pancreatic and intestinal enzymes, first into their component nucleotides and then into nitrogenous bases and monosaccharides [Fig. 2.4, p. 34]. The bases are absorbed by active transport, and the monosaccharides are absorbed by facilitated diffusion and secondary active transport, as other simple sugars are.

The Intestine Absorbs Vitamins and Minerals

In general, the fat-soluble vitamins (A, D, E, and K) are absorbed in the small intestine along with fats—one reason that health professionals are concerned about excessive consumption of "fake fats," such as Olestra, that are not absorbed. The same concern exists with orlistat (Alli®), a lipase inhibitor used for weight loss. Users of these weight-loss aids are advised to take a daily multivitamin to avoid vitamin deficiencies.

The water-soluble vitamins (C and most B vitamins) are absorbed by mediated transport. The major exception is **vitamin B_{12},** also known as *cobalamin* because it contains the element cobalt. We obtain most of our dietary supply of B_{12} from seafood, meat, and milk products. The intestinal transporter for B_{12} is found only in the ileum and recognizes B_{12} only when the vitamin is complexed with a protein called **intrinsic factor,** secreted by the same gastric parietal cells that secrete acid.

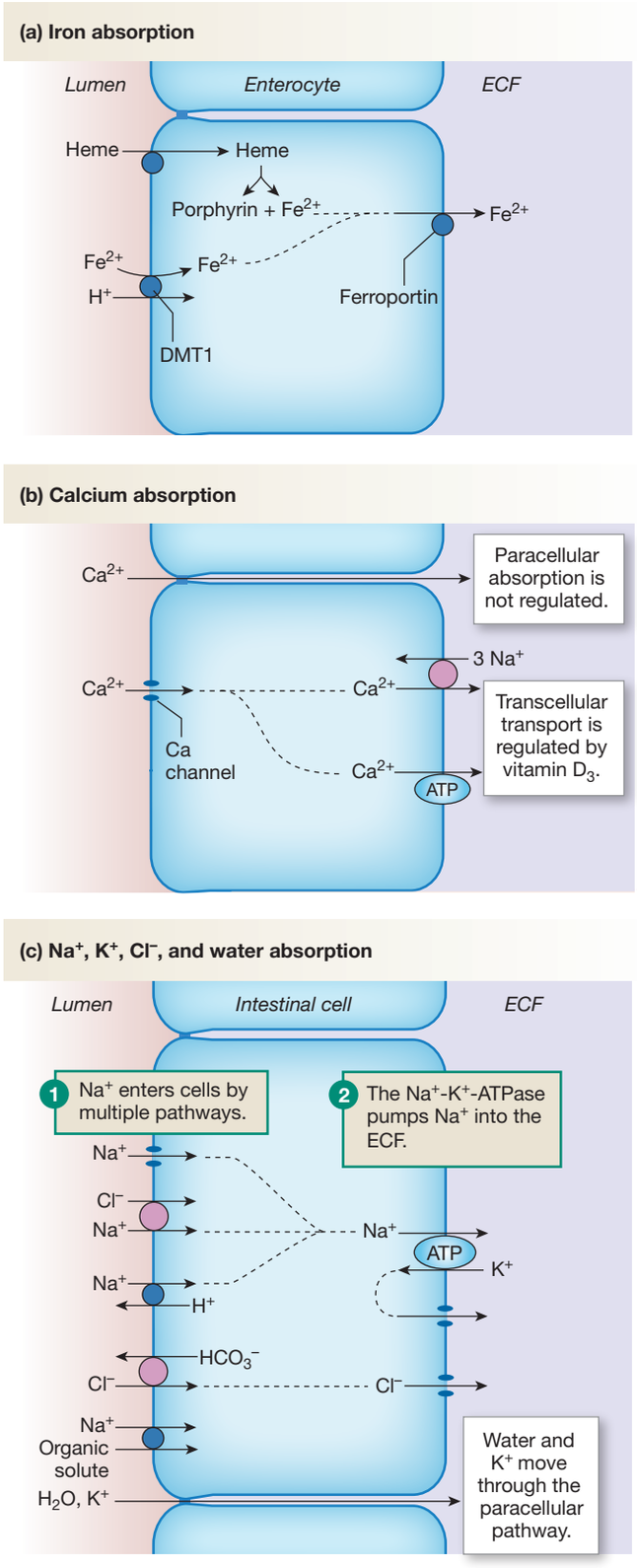
RUNNING **PROBLEM**

Rehydrating people with cholera is the key to their survival. Most patients who develop cholera can be treated successfully with oral rehydration salts. However, in about 5% of patients, the dehydration caused by cholera-induced diarrhea can be severe. If left untreated, these patients can die from circulatory collapse as soon as 18 hours after infection. Because Brooke's blood pressure was so low, the medical personnel decided that she needed intravenous (IV) fluids to restore her volume.

Q6: *Recipes for oral rehydration therapy usually include sugar (sucrose) and table salt. Explain how the sugar enhances intestinal absorption of Na^+.*

Q7: *Which type of IV solution would you select for Brooke, and why? Your choices are normal (isotonic) saline, half-normal saline, and 5% dextrose in water (D-5-W).*

FIG. 21.19 Ion and water absorption



One concern about extended use of drugs that inhibit gastric acid secretion, such as the proton-pump inhibitors discussed earlier, is that they may cause decreased absorption of vitamin B_{12}. In the complete absence of intrinsic factor, severe vitamin B_{12} deficiency causes the condition known as *pernicious anemia.* In this state, red blood cell synthesis (*erythropoiesis*), which depends on vitamin B_{12}, is severely diminished. Lack of intrinsic factor cannot be remedied directly, but patients with pernicious anemia can be given vitamin B_{12} shots.

Iron and Calcium Mineral absorption usually occurs by active transport. Iron and calcium are two of the few substances whose intestinal absorption is regulated. For both minerals, a decrease in body concentrations of the mineral leads to enhanced uptake at the intestine.

Dietary iron is ingested as heme iron [p. 521] in meat and as ionized iron in some plant products. Heme iron is absorbed by an apical transporter on the enterocyte (**FIG. 21.19a**). Ionized iron Fe^{2+} is actively absorbed by apical cotransport with H^+ on a protein called the *divalent metal transporter 1* (*DMT1*). Inside the cell, enzymes convert heme iron to Fe^{2+} and both pools of ionized iron leave the cell on a transporter called *ferroportin*.

Iron uptake by the body is regulated by a peptide hormone called *hepcidin.* When body stores of iron are high, the liver secretes hepcidin, which binds to ferroportin. Hepcidin binding causes the enterocyte to destroy the ferroportin transporter, which results in decreased iron uptake across the intestine.

Most Ca^{2+} absorption in the gut occurs by passive, unregulated movement through paracellular pathways (Fig. 21.19b). Hormonally regulated transepithelial Ca^{2+} transport takes place in the duodenum. Calcium enters the enterocyte through apical Ca^{2+} channels and is actively transported across the basolateral membrane by either a Ca^{2+}-ATPase or by the Na^+-Ca^{2+} antiporter. Calcium absorption is regulated by vitamin D_3, discussed in Chapter 23.

The Intestine Absorbs Ions and Water

Most water absorption takes place in the small intestine, with an additional 0.5 liter per day absorbed in the colon. The absorption of nutrients moves solute from the lumen of the intestine to the ECF, creating an osmotic gradient that allows water to follow.

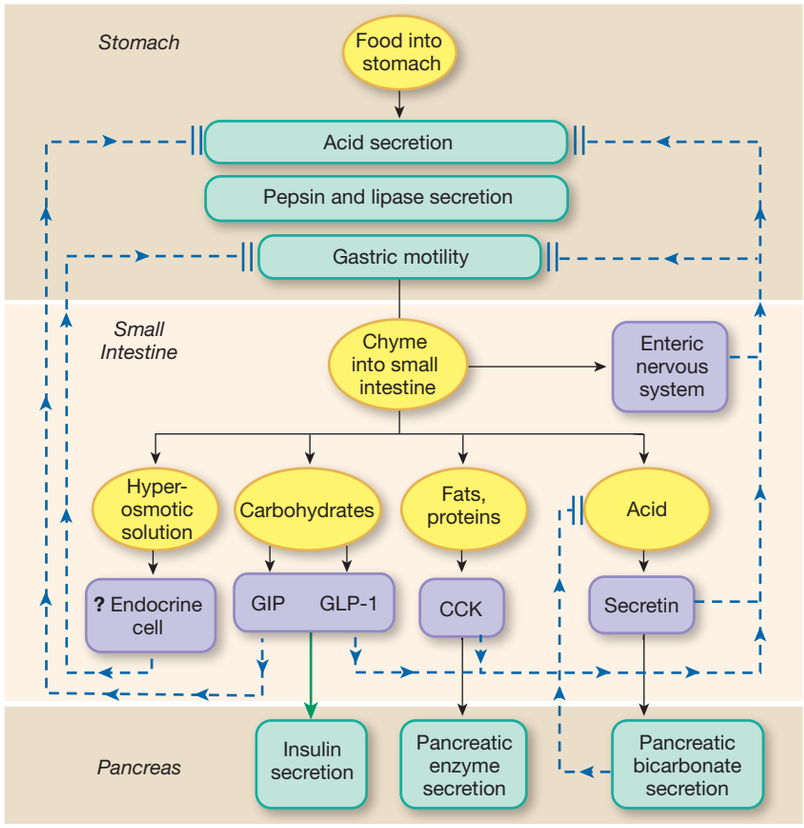
Ion absorption into the body also creates the osmotic gradients needed for water movement. Enterocytes in the small intestine and **colonocytes,** the epithelial cells on the luminal surface of the colon, absorb Na^+ using three membrane proteins (Fig. 21.19c): apical Na^+ channels such as ENaC, a Na^+-Cl^- symporter, and the Na^+-H^+ exchanger (NHE). In the small intestine, a significant fraction of Na^+ absorption also takes place through Na^+-dependent organic solute uptake, such as the SGLT and Na^+-amino acid transporters.

On the basolateral side of both enterocytes and colonocytes, the primary transporter for Na^+ is Na^+-K^+-ATPase. Chloride

FIG. 21.20 Integration of gastric and intestinal phases

Chyme moving into the duodenum triggers neural and endocrine reflexes that

1. Initiate enzyme and bicarbonate secretion; ⟶
2. Feed back to slow gastric digestion and emptying; - - ➤ - - ||
3. Feed forward to start insulin secretion. ⟶



uptake uses an apical Cl^--HCO_3^- exchanger and a basolateral Cl channel to move across the cells. Potassium and water absorption in the intestine occur primarily by the paracellular pathway.

Regulation of the Intestinal Phase

The regulation of intestinal digestion and absorption comes primarily from signals that control motility and secretion. Sensors in the intestine trigger neural and endocrine reflexes that feed back to regulate the delivery rate of chyme from the stomach, and feed forward to promote digestion, motility, and utilization of nutrients.

The control signals to the stomach and pancreas are both neural and hormonal (**FIG. 21.20**):

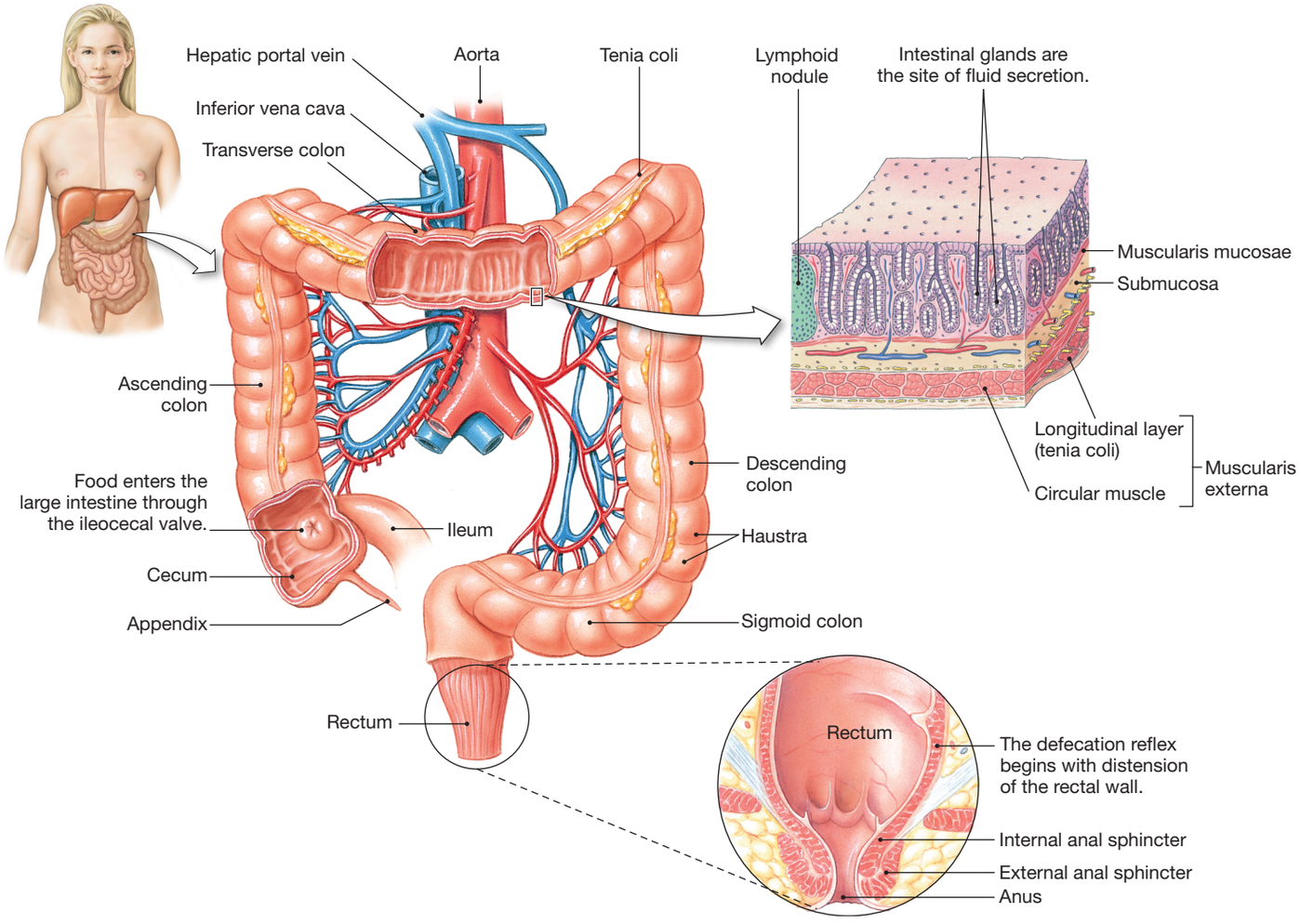
1. Chyme entering the intestine activates *the enteric nervous system,* which then decreases gastric motility and secretion and slows gastric emptying. In addition, three hormones reinforce the "decrease motility" signal: secretin, cholecystokinin (CCK), and gastric inhibitory peptide (GIP) (see Tbl. 21.1).
2. *Secretin* is released by the presence of acidic chyme in the duodenum. Secretin inhibits acid production and decreases gastric motility. In addition, secretin stimulates production of pancreatic bicarbonate to neutralize the acidic chyme that has entered the intestine.
3. *CCK* is secreted into the bloodstream if a meal contains fats. CCK also slows gastric motility and acid secretion. Because fat digestion proceeds more slowly than either protein or carbohydrate digestion, it is crucial that the stomach

EMERGING CONCEPTS

Taste Receptors in the Gut

Scientists have known for years that the GI tract has the ability to sense and respond specifically and differentially to the composition of a meal. Fats and proteins do not stimulate the same endocrine and exocrine responses as a meal of pure carbohydrate. But how does the gut "know" what is in a meal? Traditional sensory receptors, such as osmoreceptors and stretch receptors, are not tuned to respond to biomolecules. New research indicates that epithelial cells in the gut, especially some of the endocrine cells, express the same G protein-coupled receptors and the taste-linked G protein gustducin as taste buds [p. 325]. Researchers using knockout mice and cultured cell lines are now trying to establish the functional link between gut "taste receptors" and physiological responses to food.

FIG. 21.21 **Anatomy of the large intestine**



allow only small amounts of fat into the intestine at one time.

4. The *incretin hormones* GIP and glucagon-like peptide-1 (GLP-1) are released if the meal contains carbohydrates. Both hormones feed forward to promote insulin release by the endocrine pancreas, allowing cells to prepare for glucose that is about to be absorbed. They also slow the entry of food into the intestine by decreasing gastric motility and acid secretion.
5. The mixture of acid, enzymes, and digested food in chyme usually forms a hyperosmotic solution. Sensors in the intestine wall are sensitive to the osmolarity of the entering chyme. When stimulated by high osmolarity, the sensors inhibit gastric emptying in a reflex mediated by some unknown blood-borne substance.

The Large Intestine Concentrates Waste

By the end of the ileum, only about 1.5 liters of unabsorbed chyme remain. The colon absorbs most of this volume so that normally only about 0.1 liter of water is lost daily in feces. Chyme enters the large intestine through the **ileocecal valve.** This is a tonically contracted region of muscularis that narrows the opening between the ileum and the **cecum,** the initial section of the large intestine (**FIG. 21.21**). The ileocecal valve relaxes each time a peristaltic wave reaches it. It also relaxes when food leaves the stomach as part of the *gastroileal reflex.*

The large intestine has seven regions. The cecum is a dead-end pouch with the *appendix,* a small fingerlike projection, at its ventral end. Material moves from the cecum upward through the **ascending colon,** horizontally across the body through the **transverse colon,** then down through the **descending colon** and **sigmoid colon** {*sigmoeides,* shaped like a sigma, Σ}. The rectum is the short (about 12 cm) terminal section of the large intestine. It is separated from the external environment by the anus, an opening closed by two sphincters, an internal smooth muscle sphincter and an external skeletal muscle sphincter.

The wall of the colon differs from that of the small intestine in that the muscularis of the large intestine has an inner circular

layer but a discontinuous longitudinal muscle layer concentrated into three bands called the **tenia coli.** Contractions of the tenia pull the wall into bulging pockets called **haustra** {*haustrum,* bucket or scoop}.

The mucosa of the colon has two regions, like that of the small intestine. The luminal surface lacks villi and appears smooth. It is composed of colonocytes and mucus-secreting goblet cells. The crypts contain stem cells that divide to produce new epithelium, as well as goblet cells, endocrine cells, and maturing colonocytes.

Motility in the Large Intestine Chyme that enters the colon continues to be mixed by segmental contractions. Forward movement is minimal during mixing contractions and depends primarily on a unique colonic contraction known as **mass movement.** A wave of contraction decreases the diameter of a segment of colon and sends a substantial bolus of material forward. These contractions occur 3–4 times a day and are associated with eating and distension of the stomach through the *gastrocolic reflex.* Mass movement is responsible for the sudden distension of the rectum that triggers defecation.

The **defecation reflex** removes undigested feces from the body. Defecation resembles urination in that it is a spinal reflex triggered by distension of the organ wall. The movement of fecal material into the normally empty rectum triggers the reflex. Smooth muscle of the **internal anal sphincter** relaxes, and peristaltic contractions in the rectum push material toward the anus. At the same time, the external anal sphincter, which is under voluntary control, is consciously relaxed if the situation is appropriate. Defecation is often aided by conscious abdominal contractions and forced expiratory movements against a closed glottis (the *Valsalva maneuver*).

Defecation, like urination, is subject to emotional influence. Stress may increase intestinal motility and cause psychosomatic diarrhea in some individuals but may decrease motility and cause *constipation* in others. When feces are retained in the colon, either through consciously ignoring a defecation reflex or through decreased motility, continued water absorption creates hard, dry feces that are difficult to expel. One treatment for constipation is glycerin suppositories, small bullet-shaped wads that are inserted through the anus into the rectum. Glycerin attracts water and helps soften the feces to promote defecation.

Digestion and Absorption in the Large Intestine According to the traditional view of the large intestine, no significant digestion of organic molecules takes place there. However, in recent years, this view has been revised. We now know that the numerous bacteria inhabiting the colon break down significant amounts of undigested complex carbohydrates and proteins through fermentation. The end products include lactate and short-chain fatty acids, such as butyric acid. Several of these products are lipophilic and can be absorbed by simple diffusion. The fatty acids, for example, are used by colonocytes as their preferred energy substrate.

EMERGING CONCEPTS

The Human Microbiome Project

Did you realize that the average human body has many more bacteria living on and in it than it has cells? And that most of these bacteria reside in the gut? Scientists have known for decades about intestinal bacteria and the problems they cause when they leave the external environment of the gut lumen and enter the body proper. Bacterial infections are common if your appendix ruptures or if trauma, such as a stab wound, punctures the wall of the intestine. At the same time, our continued health depends on absorption of vitamins and other nutrients from bacterial metabolism. The relationship between our *microbiota* (the bacteria that inhabit our bodies) and our health has become a topic of research studies in recent years, and data are being collected by an international collaboration known as the Human Microbiome Project (*http://commonfund.nih.gov/hmp*). Do foods advertised as "probiotics" really do anything? Can bacteria influence whether we gain weight or not? Do they affect fetal development and our susceptibility to disease? We will be learning more about the answers to these questions in the years to come.

Colonic bacteria also produce significant amounts of absorbable vitamins, especially vitamin K. Intestinal gases, such as hydrogen sulfide, that escape from the gastrointestinal tract are a less useful product. Some starchy foods, such as beans, are notorious for their tendency to produce intestinal gas (**flatus**).

Diarrhea Can Cause Dehydration

Diarrhea is a pathological state in which intestinal secretion of fluid is not balanced by absorption, resulting in watery stools. Diarrhea occurs if normal intestinal water absorption mechanisms are disrupted or if there are unabsorbed osmotically active solutes that "hold" water in the lumen. Substances that cause *osmotic diarrhea* include undigested lactose and sorbitol, a sugar alcohol from plants. Sorbitol is used as an "artificial" sweetener in some chewing gums and in foods made for people with diabetes. Another unabsorbed solute that can cause osmotic diarrhea, intestinal cramping, and gas is Olestra, the "fake fat" made from vegetable oil and sugar.

In clinical settings, patients who need to have their bowels cleaned out before surgery or other procedures are often given 4 liters of an isotonic solution of polyethylene glycol and electrolytes to drink. Because polyethylene glycol cannot be absorbed, a large volume of unabsorbed solution passes into the colon, where it triggers copious diarrhea that removes all solid waste from the GI tract.

Secretory diarrheas occur when bacterial toxins, such as cholera toxin from *Vibrio cholerae* and *Escherichia coli* enterotoxin,

enhance colonic Cl^- and fluid secretion (see Fig. 21.13). When excessive fluid secretion is coupled with increased motility, diarrhea results. Secretory diarrhea in response to intestinal infection can be viewed as adaptive because it helps flush pathogens out of the lumen. However, it also has the potential to cause dehydration if fluid loss is excessive.

The World Health Organization estimates that in developing countries, 4 million people die from diarrhea each year. In the United States, diarrhea in children causes about 200,000 hospitalizations a year. Oral replacement fluids for treatment of diarrheal salt and water loss can prevent the *morbidity* (illness) and *mortality* (death) associated with diarrhea. Oral rehydration solutions usually contain glucose or sucrose as well as Na^+, K^+, and Cl^- because the inclusion of a sugar enhances Na^+ absorption. If dehydration is severe, intravenous fluid therapy may be necessary.

CONCEPT CHECK

16. In secretory diarrhea, epithelial cells in the intestinal villi may be damaged or may slough off. In these cases, would it be better to use an oral rehydration solution containing glucose or one containing sucrose? Explain your reasoning.

IMMUNE FUNCTIONS OF THE GI TRACT

As you learned at the beginning of the chapter, the GI tract is the largest immune organ in the body. Its luminal surface is continuously exposed to disease-causing organisms, and the immune cells of the GALT must prevent these pathogens from entering the body through delicate absorptive tissues. The first lines of defense are the enzymes and immunoglobulins in saliva and the highly acidic environment of the stomach. If pathogens or toxic materials make it into the small intestine, sensory receptors and the immune cells of the GALT respond. Two common responses are diarrhea, just described, and vomiting.

M Cells Sample Gut Contents

The immune system of the intestinal mucosa consists of immune cells scattered throughout the mucosa, clusters of immune cells in Peyer's patches (see Fig. 21.1f), and specialized epithelial cells called **M cells** that overlie the Peyer's patches. The M cells provide information about the contents of the lumen to the immune cells of the GALT.

The microvilli of M cells are fewer in number and more widely spaced than in the typical intestinal cell. The apical surface of M cells contains clathrin-coated pits [p. 148] with embedded membrane receptors. When antigens bind to these receptors, the M cell uses transcytosis to transport them to its basolateral membrane, where they are released into the interstitial fluid. Macrophages and lymphocytes [p. 514] are waiting in the extracellular compartment for the M cell to present them with antigens.

If the antigens are substances that threaten the body, the immune cells swing into action. They secrete cytokines to attract additional immune cells that can attack the invaders and cytokines that trigger an inflammatory response. A third response to cytokines is increased secretion of Cl^-, fluid, and mucus to flush the invaders from the GI tract.

In *inflammatory bowel diseases* (such as ulcerative colitis and Crohn's disease), the immune response is triggered inappropriately by the normal contents of the gut. One apparently successful experimental therapy for these diseases involves blocking the action of cytokines released by the gut-associated lymphoid tissues.

How certain pathogenic bacteria cross the barrier created by the intestinal epithelium has puzzled scientists for years. The discovery of M cells may provide the answer. It appears that some bacteria, such as *Salmonella* and *Shigella,* have evolved surface molecules that bind to M cell receptors. The M cells then obligingly transport the bacteria across the epithelial barrier and deposit them inside the body, where the immune system immediately reacts. Both bacteria cause diarrhea, and *Salmonella* also causes fever and vomiting.

Vomiting Is a Protective Reflex

Vomiting, or *emesis,* the forceful expulsion of gastric and duodenal contents from the mouth, is a protective reflex that removes toxic materials from the GI tract before they can be absorbed. However, excessive or prolonged vomiting, with its loss of gastric acid, can cause metabolic alkalosis [p. 647].

The vomiting reflex is coordinated through a vomiting center in the medulla. The reflex begins with stimulation of sensory receptors and is often (but not always) accompanied by nausea. A variety of stimuli from all over the body can trigger vomiting. They include chemicals in the blood, such as cytokines and certain drugs; pain; disturbed equilibrium, such as occurs in a moving car or rocking boat, and emotional stress. Tickling the back of the pharynx can also induce vomiting.

Efferent signals from the vomiting center initiate a wave of reverse peristalsis that begins in the small intestine and moves upward. The motility wave is aided by abdominal contraction that increases intra-abdominal pressure. The stomach relaxes so that the increased pressure forces gastric and intestinal contents back into the esophagus and out of the mouth.

During vomiting, respiration is inhibited. The epiglottis and soft palate close off the trachea and nasopharynx to prevent the *vomitus* from being inhaled (*aspirated*). Should acid or small food particles get into the airways, they could damage the respiratory system and cause *aspiration pneumonia.*

RUNNING PROBLEM CONCLUSION | Cholera in Haiti

Vibrio cholerae, the bacterium that causes cholera, was first identified in India in the 1800s. It has caused seven worldwide epidemics in the years since. About 75% of people who become infected with *V. cholerae* have no symptoms, but the remaining 25% develop potentially fatal *secretory diarrhea*. The gut immune systems in most people overcome the infection within about a week. But until that happens, even asymptomatic people shed the bacteria in their feces, which contributes to the spread of the disease. In Haiti, plagued by inadequate sanitation and an earthquake-damaged water supply, cholera spread rapidly. By November 2013, nearly 700,000 cases and more than 8,000 deaths had been reported. Genetic analysis of the *Vibrio cholera* strain in Haiti suggests that the bacterium was accidentally brought to the island by asymptomatic United Nations peacekeepers from Asia.

To learn more about cholera in Haiti, see the CDC (*www.cdc.gov*) and WHO (*www.who.int*) web sites. If you plan to travel to Haiti or any place with a declared cholera epidemic, visit *www.cdc.gov/travel* and review proper guidelines and procedures on avoiding contact with this potentially lethal bacterium. Now check your understanding of this running problem by comparing your answers to the information in the following summary table.

Question	Facts	Integration and Analysis
Q1: *What would you expect Brooke's ECF volume to be?*	Most fluid in diarrhea has been secreted from the body into the lumen of the GI tract.	Loss of fluid from the body would decrease ECF volume.
Q2: *Why was Brooke experiencing a rapid heartbeat?*	Loss of ECF volume with the diarrhea decreased Brooke's blood pressure.	Decreased blood pressure triggered a baroreceptor reflex [p. 493]. Increased sympathetic and decreased parasympathetic output to the SA node resulted in a faster heart rate.
Q3: *Esomeprazole is a proton pump inhibitor (PPI). For what symptom or condition might Brooke have been taking this drug?*	"Proton pump" is another name for an ATP-dependent H^+ transporter. Stomach acid is secreted by H^+-K^+-ATPase.	A proton pump inhibitor would decrease stomach acid, so Brooke may have been taking the PPI for heartburn or gastroesophageal reflex disorder (GERD).
Q4: *Why might taking a protein pump inhibitor like esomeprazole have increased Brooke's chances of contracting cholera?*	Proton pump inhibitors decrease the acidity in the stomach. Low gastric pH is one of the body's defense mechanisms.	In a less acidic stomach environment, more cholera bacteria might survive passage through the stomach to the small intestine, where they could infect the enterocytes.
Q5: *Why would continuously open enterocyte CFTR channels cause secretory diarrhea and dehydration in humans?*	Chloride leaves enterocytes by the CFTR channel. Na^+ and water follow by the paracellular pathway. See Figure 21.13.	A continuously open CFTR channel means increased secretion of NaCl and water into the lumen, which leads to watery diarrhea. The salt and water come from the ECF, and their loss causes dehydration.
Q6: *Recipes for oral rehydration therapy usually include sugar (sucrose) and table salt. Explain how the sugar enhances intestinal absorption of Na^+.*	Sucrose is digested to glucose and fructose. Glucose is absorbed by Na^+-dependent indirect active transport on the SGLT.	Na^+ uptake by the SGLT provides an additional pathway for Na^+ absorption and speeds the replenishing of fluid loss.
Q7: *Which type of IV solution would you select for Brooke and why? Your choices are normal (isotonic) saline, half-normal saline, and 5% dextrose in water (D-5-W).*	Chloride secretion by enterocytes causes Na^+ and water to follow, with the net result being secretion of isotonic fluid. The replacement fluid should match the fluid loss as closely as possible.	Normal saline (isosmotic) approximates the fluid lost in cholera diarrhea. Half-normal saline would dilute the body's osmolarity. D-5-W is not acceptable because it is equivalent to giving pure water and would not replace the lost NaCl.

This problem was written by Claire Conroy when she was an undergraduate Nutritional Sciences/Pre-Physical Therapy student at the University of Texas at Austin.

CHAPTER SUMMARY

The digestive system, like the renal system, plays a key role in *mass balance* in the body. Most material that enters the system, whether by mouth or by secretion, is absorbed before it reaches the end of the GI tract. In pathologies such as diarrhea, in which absorption and secretion are unbalanced, the loss of material through the GI tract can seriously disrupt *homeostasis.* Absorption and secretion in the GI tract provide numerous examples of *movement across membranes,* and most transport processes follow patterns you have encountered in the kidney and other systems. Finally, regulation of GI tract function illustrates the complex interactions that take place between endocrine and neural *control systems* and the immune system.

Anatomy of the Digestive System

GI: Anatomy Review

1. Food entering the digestive system passes through the mouth, pharynx, **esophagus, stomach (fundus, body, antrum), small intestine (duodenum, jejunum, ileum), large intestine (colon, rectum),** and **anus.** (p. 658; Fig. 21.1a)
2. The **salivary glands, pancreas,** and **liver** add exocrine secretions containing enzymes and mucus to the lumen. (p. 655; Fig. 21.1a)
3. **Chyme** is a soupy substance created as ingested food is broken down by mechanical and chemical digestion. (p. 655)
4. The wall of the GI tract consists of four layers: mucosa, submucosa, muscle layers, and serosa. (p. 658; Fig. 21.1d)
5. The **mucosa** faces the lumen and consists of epithelium, the **lamina propria,** and the **muscularis mucosae.** The lamina propria contains immune cells. Small **villi** and invaginations increase the surface area. (p. 658; Fig. 21.1e, f)
6. The **submucosa** contains blood vessels and lymph vessels and the **submucosal plexus** of the **enteric nervous system.** (p. 659; Fig. 21.1f)
7. The **muscularis externa** consists of a layer of circular muscle and a layer of longitudinal muscle. The **myenteric plexus** lies between these two muscle layers. (p. 659; Fig. 21.1e, f)
8. The **serosa** is the outer connective tissue layer that is a continuation of the peritoneal membrane. (p. 659; Fig. 21.1d)

Digestive Function and Processes

GI: Secretion, Digestion and Absorption, Motility

9. The GI tract moves nutrients, water, and electrolytes from the external environment to the internal environment. (p. 659)
10. **Digestion** is chemical and mechanical breakdown of foods into absorbable units. **Absorption** is transfer of substances from the lumen of the GI tract to the ECF. **Motility** is movement of material through the GI tract. **Secretion** is the transfer of fluid and electrolytes from ECF to lumen or the release of substances from cells. (p. 659; Fig. 21.2)
11. About 2 L of fluid per day enter the GI tract through the mouth. Another 7 L of water, ions, and proteins are secreted by the body. To maintain mass balance, nearly all of this volume is reabsorbed. (p. 661; Fig. 21.3)
12. Many digestive enzymes are secreted as inactive zymogens to prevent autodigestion. (p. 661)
13. For defense from invaders, the GI tract contains the largest collection of lymphoid tissue in the body, the **gut-associated lymphoid tissue (GALT).** (p. 660)
14. GI smooth muscle cells depolarize spontaneously and are electrically connected by gap junctions. Some segments of the gut are **tonically contracted,** but others exhibit **phasic contractions.** (p. 661)
15. Intestinal smooth muscle exhibits spontaneous **slow wave potentials** that originate in the **interstitial cells of Cajal.** (p. 661)
16. When a slow wave reaches threshold, it fires action potentials and the muscle contracts. (p. 663; Fig. 21.4a)
17. Between meals, the **migrating motor complex** moves food remnants from the upper GI tract to the lower regions. (p. 663; Fig. 21.4b)
18. **Peristaltic contractions** are progressive waves of contraction that occur mainly in the esophagus. **Segmental contractions** are mixing contractions. (p. 663; Fig. 21.4c, d)

Regulation of GI Function

GI: Control of the Digestive System

19. The **enteric nervous system** can integrate information without input from the CNS. **Intrinsic neurons** lie completely within the ENS. (p. 664)
20. **Short reflexes** originate in the ENS and are integrated there. **Long reflexes** may originate in the ENS or outside it but are integrated in the CNS. (p. 664; Fig. 21.5)
21. Generally, parasympathetic innervation is excitatory for GI function, and sympathetic innervation is inhibitory. (p. 665)
22. GI peptides excite or inhibit motility and secretion. Most stimuli for GI peptide secretion arise from the ingestion of food. (p. 665)
23. GI hormones are divided into the gastrin family (**gastrin, cholecystokinin**), secretin family (**secretin, gastric inhibitory peptide, glucagon-like peptide-1**), and hormones that do not fit into either of those two families (**motilin**). (p. 665, 667; Tbl. 21.1)

The Cephalic Phase

24. The sight, smell, or taste of food initiates GI reflexes in the **cephalic phase** of digestion. (p. 668; Fig. 21.8)
25. Mechanical digestion begins with chewing, or **mastication.** Saliva moistens and lubricates food. Salivary amylase digests carbohydrates. (p. 668)

26. **Saliva** is an exocrine secretion that contains water, ions, mucus, and proteins. Salivation is under autonomic control. (p. 668)
27. Swallowing, or **deglutition,** is a reflex integrated by a medullary center. (p. 668; Fig. 21.7)

The Gastric Phase

28. The stomach stores food, begins protein and fat digestion, and protects the body from swallowed pathogens. (p. 669)
29. The stomach secretes mucus and bicarbonate from **mucous cells,** pepsinogen from **chief cells,** somatostatin from **D cells,** histamine from **ECL cells,** and gastrin from **G cells.** (p. 670, 672; Fig. 21.9a, b; Fig. 21.10)
30. **Parietal cells** in gastric glands secrete hydrochloric acid. (p. 670; Fig. 21.9c)
31. Gastric function is integrated with the cephalic and intestinal phases of digestion. (p. 670; Fig. 21.8, Fig. 21.20)

The Intestinal Phase

32. Most nutrient absorption takes place in the small intestine. The large intestine absorbs water and ions. (p. 673)
33. Most absorbed nutrients go directly to the liver via the hepatic portal system before entering the systemic circulation. (p. 673; Fig. 21.12)
34. Intestinal enzymes are part of the **brush border. Goblet cells** secrete mucus. (p. 673)
35. Intestinal cells secrete an isotonic NaCl solution using the **CFTR chloride channel.** Water and Na^+ follow Cl^- down osmotic and electrochemical gradients. (p. 674; Fig. 21.13)
36. The pancreas secretes a watery $NaHCO_3$ solution from duct cells and inactive digestive enzymes from the acini. (p. 674; Fig. 21.14)
37. Bile made by **hepatocytes** contains **bile salts,** bilirubin, and cholesterol. Bile is stored and concentrated in the gallbladder (p. 675; Fig. 21.15)
38. Fat digestion is facilitated by bile salts. As digestion proceeds, fat droplets form **micelles.** (p. 675; Fig. 21.16)
39. Fat digestion requires the enzyme **lipase** and the cofactor **colipase.** (p. 678; Fig. 21.16)
40. Fat absorption occurs primarily by simple diffusion. Cholesterol is actively transported. (p. 676; Fig. 21.16)
41. **Chylomicrons,** made of monoglycerides, fatty acids, cholesterol, and proteins, are absorbed into the lymph. (p. 678; Fig. 21.16)
42. **Amylase** digests starch to maltose. **Disaccharidases** digest disaccharides to monosaccharides. (p. 680; Fig. 21.17)
43. Glucose absorption uses the SGLT Na^+-glucose symporter and GLUT2 transporter. Fructose uses the GLUT5 and GLUT2 transporters. (p. 680; Fig. 21.17)
44. **Endopeptidases** (also called proteases) break proteins into smaller peptides. **Exopeptidases** remove amino acids from peptides. (p. 681; Fig. 21.18)
45. Amino acids are absorbed via Na^+- or H^+-dependent cotransport. Dipeptides and tripeptides are absorbed via H^+-dependent cotransport. Some larger peptides are absorbed intact via transcytosis. (p. 682; Fig. 21.18)
46. Nucleic acids are digested and absorbed as nitrogenous bases and monosaccharides. (p. 682)
47. Fat-soluble vitamins are absorbed along with fats. Water-soluble vitamins are absorbed by mediated transport. Vitamin B_{12} absorption requires **intrinsic factor** secreted by the stomach. (p. 682)
48. Mineral absorption usually occurs via active transport. Some calcium moves by the paracellular pathway. Ions and water move by the paracellular pathway as well as by membrane proteins. (p. 682; Fig. 21.19)
49. Acid in the intestine, CCK, and secretin delay gastric emptying. (p. 684; Fig. 21.20)
50. Undigested material in the colon moves forward by **mass movement.** The **defecation reflex** is triggered by sudden distension of the rectum. (p. 686; Fig. 21.21)
51. Colonic bacteria use fermentation to digest organic material. (p. 686)
52. Cells of the colon can both absorb and secrete fluid. Excessive fluid secretion or decreased absorption causes diarrhea. (p. 686)

Immune Functions of the GI Tract

53. Protective mechanisms of the GI tract include acid and mucus production, vomiting, and diarrhea. (p. 687)
54. **M cells** sample gut contents and present antigens to cells of the GALT. (p. 687)
55. **Vomiting** is a protective reflex integrated in the medulla. (p. 687)

REVIEW QUESTIONS

In addition to working through these questions and checking your answers on p. A-28, review the Learning Outcomes at the beginning of this chapter.

Level One Reviewing Facts and Terms

1. Match each of the following descriptions with the appropriate term(s):

a. chyme is produced here	1. colon
b. organ where most digestion occurs	2. stomach
c. initial section of small intestine	3. small intestine
d. this adds exocrine secretions to duodenum via a duct	4. duodenum
e. sphincter between stomach and intestine	5. ileum
f. enzymes produced here	6. jejunum
g. distension of its walls triggers the defecation reflex	7. pancreas
	8. pylorus
	9. rectum
	10. liver

2. For most nutrients, which two processes are not regulated? Which two are continuously regulated? Why do you think these differences exist? Defend your answer.
3. Define the four basic processes of the digestive system and give an example of each.
4. List the four layers of the GI tract walls. What type of tissue predominates in each layer?
5. Describe the functional types of epithelium lining the stomach and intestines.
6. What are Peyer's patches? M cells of the intestine?

7. What purposes does motility serve in the gastrointestinal tract? Which types of tissue contribute to gut motility? Which types of contraction do the tissues undergo?
8. What is a zymogen? What is a proenzyme? List two examples of each.
9. Match each of the following cells with the product(s) it secretes. Items may be used more than once.

a. parietal cells	1. enzymes
b. goblet cells	2. histamine
c. brush border cells	3. mucus
d. pancreatic cells	4. pepsinogen
e. D cells	5. gastrin
f. ECL cells	6. somatostatin
g. chief cells	7. HCO_3^-
h. G cells	8. HCl
	9. intrinsic factor

10. How does each of the following factors affect digestion? Briefly explain how and where each factor exerts its effects.
    (a) emulsification
    (b) neural activity
    (c) low pH
    (d) size of food particles
11. Most digested nutrients are absorbed into the _____ of the _____ system, delivering nutrients to the _____ (organ). However, digested fats go into the _____ system because intestinal capillaries have a(n) _____ around them that most lipids are unable to cross.
12. What is the enteric nervous system, and what is its function?
13. What are short reflexes? What types of responses do they regulate? What is meant by the term *long reflex?*
14. What role do paracrines play in digestion? Give specific examples.

Level Two Reviewing Concepts

15. Mapping. **Map 1:** List the three major groups of biomolecules across the top of a large piece of paper. Down the left side of the paper write *mouth, stomach, small intestine.* For each biomolecule in each location, fill in the enzymes that digest the biomolecule, the products of digestion for each enzyme, and the location and mechanisms by which these products are absorbed.

    Map 2: Create a diagram or map using the following terms related to iron absorption:

• DMT1	• heme iron
• endocytosis	• hepcidin
• enterocyte	• Fe^{2+}
• ferroportin	• liver

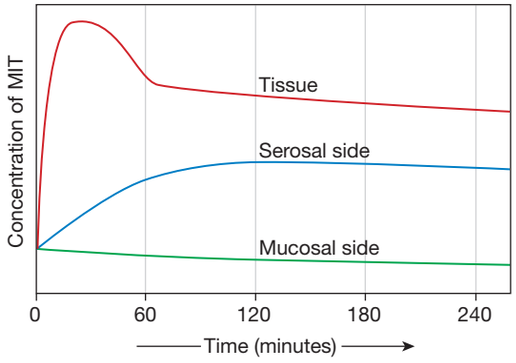
16. Define, compare, and contrast the following pairs or sets of terms:
    (a) mastication, deglutition
    (b) microvilli, villi
    (c) peristalsis, segmental contractions, migrating motor complex, mass movements
    (d) chyme, feces
    (e) short reflexes, long reflexes
    (f) submucosal plexus, myenteric plexus, vagus nerve
    (g) cephalic, gastric, and intestinal phases of digestion
17. (a) Diagram the cellular mechanisms by which Na^+, K^+, and Cl^- are reabsorbed from the intestine.
    (b) Diagram the cellular mechanisms by which H^+ and HCO_3^- are secreted into the lumen.
18. Compare the enteric nervous system with the cephalic brain. Give some specific examples of neurotransmitters, neuromodulators, and supporting cells in the two.
19. List and briefly describe the actions of the members of each of the three groups of GI hormones.
20. Explain how H_2 receptor antagonists and proton pump inhibitors decrease gastric acid secretion.

Level Three Problem Solving

21. In the disease state called *hemochromatosis,* the hormone hepcidin is either absent or not functional. Use your understanding of iron homeostasis to predict what would happen to intestinal iron uptake and plasma levels of iron in this disease.
22. Erica's baby, Justin, has had a severe bout of diarrhea and is now dehydrated. Is his blood more likely to be acidotic or alkalotic? Why?
23. Mary Littlefeather arrives in her physician's office complaining of severe, steady pain in the upper right quadrant of her abdomen. The pain began shortly after she ate a meal of fried chicken, French fries, and peas. Lab tests and an ultrasound reveal the presence of gallstones in the common bile duct running from the liver, gallbladder, and pancreas into the small intestine.
    (a) Why was Mary's pain precipitated by the meal she ate?
    (b) Which of the following processes will be affected by the gallstones: micelle formation in the intestine, carbohydrate digestion in the intestine, and protein absorption in the intestine. Explain your reasoning.
24. Using what you have learned about epithelial transport, draw a picture of the salivary duct cells and lumen. Arrange the following membrane channels and transporters on the apical and basolateral membranes so that the duct cell absorbs Na^+ and secretes K^+: ENaC, Na^+-K^+-ATPase, and K^+ leak channel. With neural stimulation, the flow rate of saliva can increase from 0.4 mL/min to 2 mL/min. What do you think happens to the Na^+ and K^+ content of saliva at the higher flow rate?

Level Four Quantitative Problems

25. Intestinal transport of the amino acid analog MIT (monoiodotyrosine) can be studied using the "everted sac" preparation. A length of intestine is turned inside out, filled with a solution containing MIT, tied at both ends, and then placed in a bath containing nutrients, salts, and an equal concentration of MIT. Changes in the concentration of MIT are monitored in the bath (mucosal or apical side of the inverted intestine), in the intestinal cells (tissue), and within the sac (serosal or basolateral side of the intestine) over a 240-minute period. The results are displayed in the graph shown here. (Data from Nathans *et al.*, *Biochimica et Biophysica Acta 41:* 271–282, 1960.)



(a) Based on the data shown, is the transepithelial transport of MIT a passive process or an active process?
(b) Which way does MIT move: (1) apical to tissue to basolateral, or (2) basolateral to tissue to apical? Is this movement absorption or secretion?
(c) Is transport across the apical membrane active or passive? Explain your reasoning.
(d) Is transport across the basolateral membrane active or passive? Explain your reasoning.

Answers to Concept Checks, Figure and Graph Questions, and end-of-chapter Review Questions can be found in Appendix A [p. A-1].