

CHAPTER 2

Digestion and Absorption

← HERE'S WHERE YOU HAVE BEEN

1. The basic unit of human life is the cell, which operates independently and in concert with other cells to sustain human life.
2. There are approximately 200 different types of cells in the human body, each one with different roles and nutrient requirements.
3. Cell structural and operational components have specialized functions that affect nutrient processing, storage, and requirements.
4. Many nutrients play a role in protein synthesis by influencing gene expression or various steps in protein manufacturing.
5. Proteins have many specialized functions, including serving as enzymes, transporters, receptors, and hormones.

HERE'S WHERE YOU ARE GOING →

1. Digestion is a complex synergy of the physical actions of chewing, mixing, and movement and the chemical actions of acids, enzymes, and detergent-like emulsifiers.
2. Absorption refers to the movement of nutrients from the digestive tract into the blood or lymphatic circulation, whereas the concept of bioavailability also includes the uptake and use of a nutrient by cells or tissue.
3. Perceptions of hunger and satiety involve multiple hormonal and neurologic signals, including cholecystokinin, neuropeptide Y, ghrelin, obestatin, insulin, and leptin.
4. Different types of bacteria are found throughout the entire digestive tract; the specific conditions of the different segments (e.g., mouth, stomach, colon) determine which species will thrive.

► Introduction

With the exception of intravenous infusion, nutrient entry into the body takes place by way of the gastrointestinal, or alimentary, tract. This tract is basically a tube that extends from the mouth to the anus, and the lumen is considered to be outside of the body

(**FIGURE 2.1**). The gastrointestinal tract, or simply “the gut,” and several organs (the salivary glands, pancreas, liver, and gallbladder) that empty supportive substances into the gut make up the gastrointestinal system. The primary objectives of the gastrointestinal system are to break down complex food components into substances appropriate for absorption into the body as well as

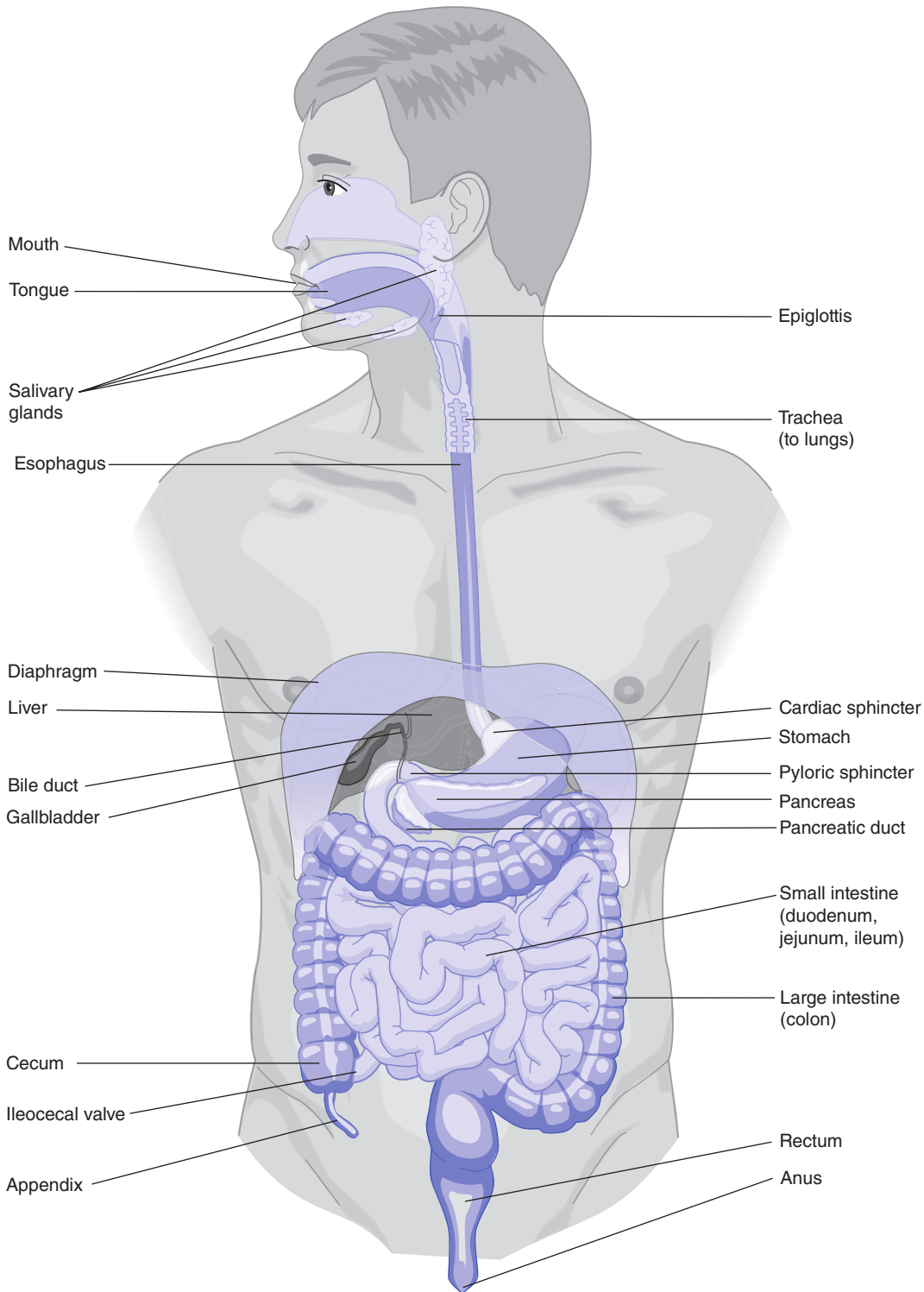


FIGURE 2.1 The Human Digestive System. Major organs and structures of the human body involved in food digestion and nutrient absorption.

to provide a means of waste removal from digestive and metabolic operations. To meet those objectives, the gastrointestinal system must engage in digestive, motility, secretory, and absorptive operations.

► Gastrointestinal Anatomy

From a histologic perspective, the wall of the gastrointestinal tract is fairly consistent throughout its length (**FIGURE 2.2**). Although some variation does exist, allowing the specialized operations inherent to different segments of the gastrointestinal tract, the structure of the wall can be discussed in general terms. The gastrointestinal tract wall is characterized by several distinct layers. The layer closest to the lumen is the mucosa. The outermost region of the mucosa, the muscularis mucosae, is mostly composed of smooth muscle. Adjacent to the muscularis mucosae is the submucosa. Situated outside of the submucosa is a layer of circular smooth muscle that is covered by a layer of longitudinal smooth muscle. The outermost layer of the gastrointestinal wall is the serosa. Buried within the different layers of the gastrointestinal tract wall are blood vessels, which transport nutrients, oxygen, and hormones to and from the wall, as well as nerve plexuses, which control wall activity.

Mouth

The mouth and the pharynx provide entry to the gastrointestinal tract. Several secretory glands located in the mouth release saliva, which begins the chemical

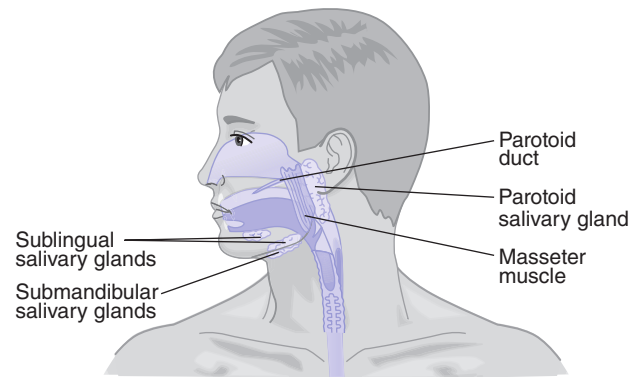


FIGURE 2.3 Location of Primary Salivary Glands.

Glands responsible for saliva production and some enzymes to initiate food digestion. Masseter muscle aids in mastication, or chewing of food.

digestion of food while also supporting chewing (mastication) and swallowing (deglutination) mechanisms (**FIGURE 2.3**). Swallowed content enters the stomach by traversing the 25-centimeter (10-inch) muscular esophagus. The esophagus ends with a thickened muscular ring called the lower esophageal sphincter (LES) or cardiac sphincter, with respect to its close anatomic proximity to the heart.

Stomach

The stomach is approximately 25 centimeters long and is J-shaped, with its curvature toward the right (**FIGURE 2.4**). It is situated just beneath the diaphragm and is separated from the esophagus by the

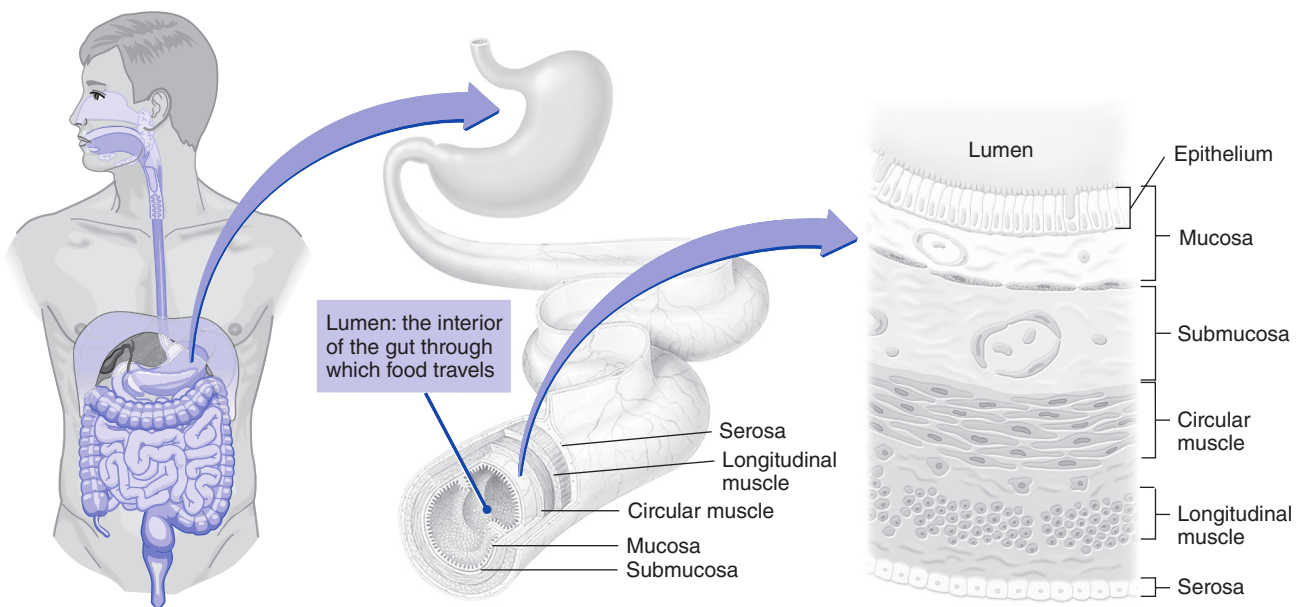


FIGURE 2.2 General Anatomic Structure of the Digestive Tract Wall. Illustration on the epithelium, mucosa, submucosa, circular muscle, longitudinal muscle, and serosa that comprise the digestive tract.

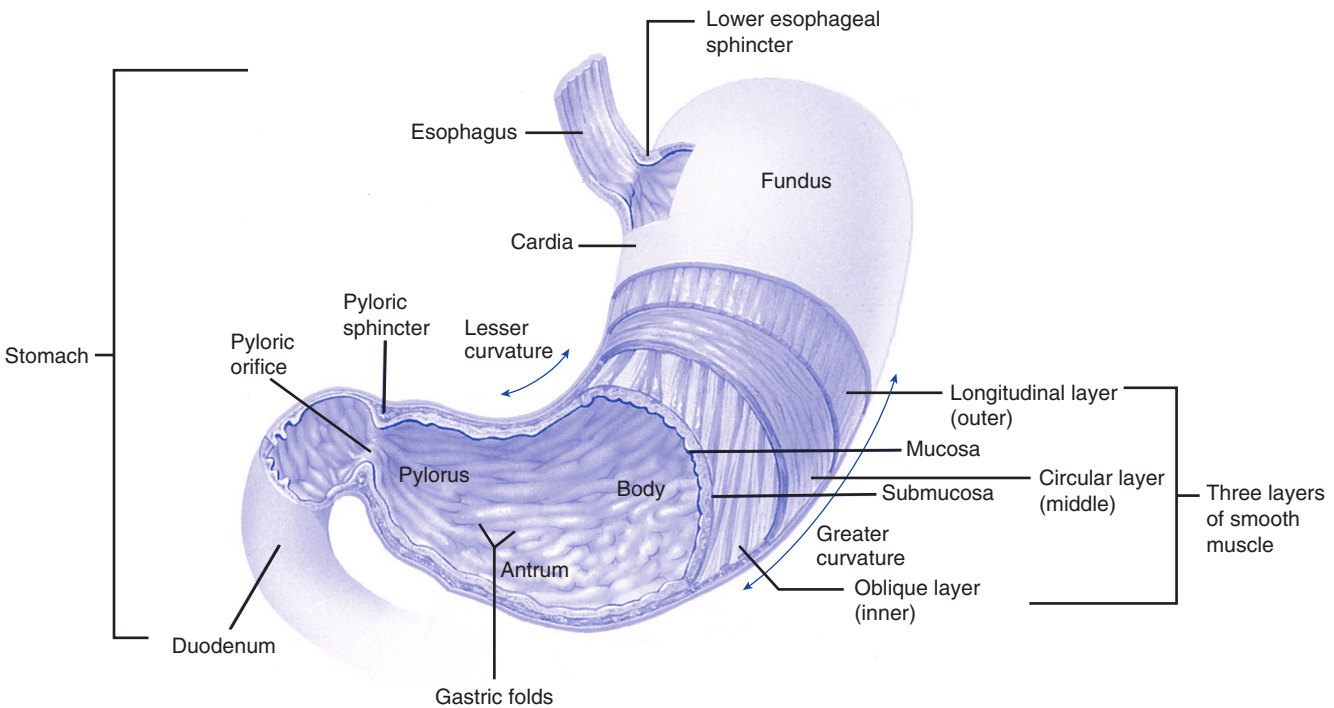


FIGURE 2.4 The Stomach. Areas of the stomach: fundus, cardia, and antrum. Note that the stomach structures, including sphincter muscles and cross-sectional views of the mucosa, submucosa, and muscles.

LES; distally, the stomach is separated from the small intestine by another smooth muscular ring called the **pyloric sphincter**. The volume of an empty adult stomach is only about 50 milliliters (about 1.67 ounces); however, it can accommodate as much as 1.5 liters (52 ounces) or more during a meal.

The stomach is subdivided into three segments: the fundus, cardia (or body), and antrum. Those segments and their walls are characterized by the presence of several exocrine and endocrine glands. The oxyntic glands are the primary type of **gastric** gland;

those structures contain exocrine cells that secrete a hydrochloric acid (HCl) solution, pepsinogen, intrinsic factor, mucus, and other substances (**FIGURE 2.5**). The density of the glands, along with the histology, can vary regionally in the stomach.

Small Intestine

The contents of the stomach are slowly released into the small intestine, which is approximately 3 meters (10 feet) in length and can be divided into three

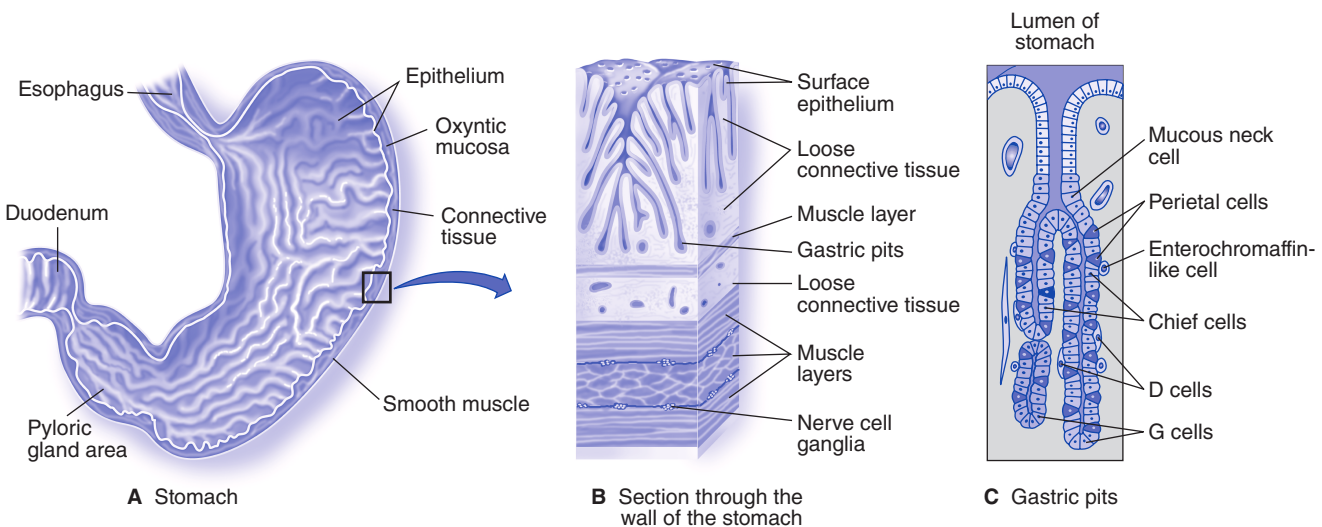


FIGURE 2.5 Oxyntic Glands. The oxyntic glands of the stomach secrete hydrochloric acid (HCl), pepsinogen, intrinsic factor, mucus, and other substances into the lumen of the stomach.

segments. The **duodenum** is the most proximal segment to the stomach and is typically approximately 30 centimeters (1 foot) in length. Secretions from the liver and gallbladder, via the hepatic bile ducts and cystic duct, respectively, combine in the common bile duct, which empties into the duodenum through the sphincter of Oddi. Secretions from the pancreas, via the pancreatic duct, flow into the terminal aspect of the common bile duct and subsequently flow into the duodenum via the sphincter of Oddi. The **jejunum** and the ileum, in that order, are the distal segments of the small intestine and combine for approximately 2.75 meters (9 feet) in length.

Rugae, Villi, and Microvilli

The small intestine is the primary site of digestion and absorption in the gastrointestinal tract. To optimize digestive and absorptive operations, the surface area of the small intestine wall is greatly enhanced by three mucosal modifications. First, the small intestine wall is thrown into folds (rugae) called valvulae conniventes (folds of Kerckring). Those semicircular folds, which extend as much as 8 millimeters into the lumen, increase the surface area of the small intestine wall 3-fold (**FIGURE 2.6**). Next, millions of fingerlike projections called **villi** protrude from the small intestine wall and enhance the surface area another 10-fold. The villi themselves are lined primarily with small intestine epithelial cells called enterocytes, which are highly specialized for digestive and absorptive operations.

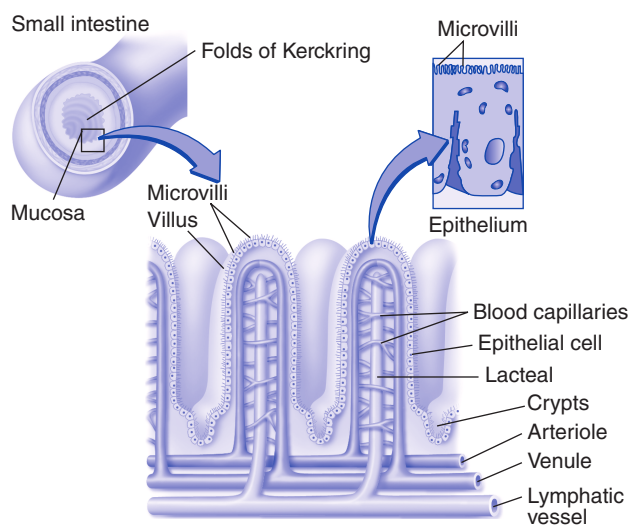


FIGURE 2.6 Three Levels of Folding of the Small Intestine. The folds of Kerckring are merely a folding of the mucosa. Extending from the folds of Kerckring are fingerlike projections (villi) that are lined with enterocytes. The luminal face of the plasma membrane of enterocytes has thousands of bristle-like extensions called microvilli.

Finally, the plasma membranes of the enterocytes contain fine evaginations called **microvilli** on their luminal surface. A single enterocyte may contain approximately 1700 microvilli, each typically being about 1 micrometer in length and 0.1 micrometer in diameter. Microscopically, this gives the lining of the small intestine a brush border appearance. Microvilli expand the surface area another 20-fold. Cumulatively, the folds of Kerckring, villi, and microvilli enhance the surface area of the small intestine about 600 times, to approximately 300 square meters, or roughly the size of a tennis court.

In the gastrointestinal tract, villi are unique to the small intestine and are specifically designed to provide nutrients entrance to the body. Internally, each villus contains a capillary and a central lacteal, which together provide the means for nutrient absorption (see Figure 2.6). In general, small absorbed water-soluble substances will enter the systemic circulation by crossing the capillary wall. In contrast, most absorbed lipid-soluble substances are destined to enter the blood indirectly by first draining into the central lacteal as part of a **lipoprotein** (chylomicron) and flowing through the lymphatic circulation.

In the depths between villi are the crypts of Lieberkühn. The cells found in these crypts undergo rapid mitosis, and the new cells then migrate up the villi to allow continual replacement of enterocytes that are being sloughed off the tip of the villi. Enterocyte turnover is approximately 3 to 5 days. Other cells in the crypts include protein-secreting Paneth cells, mucus-secreting goblet cells, and enterochromaffin cells, which perform endocrine activities. Finally, lymphoid tissue, called Peyer patches, is also found in the wall of the small intestine and contains both T lymphocytes and B lymphocytes. Peyer patches provide a line of defense against bacteria and other ingested foreign substances.

Large Intestine (Colon)

The small intestine is separated from the large intestine, or **colon**, by the ileocecal valve. The large intestine is approximately 1.5 to 1.8 meters (5 to 6 feet) long, with an average diameter of 6 centimeters (~2.5 inches); the diameter decreases moving distally. The large intestine can be segmented, in order, into the cecum, colon, rectum, and anal canal. With respect to the directional movement of content through the colon in an upright human, regions of the colon are often referred to as ascending, transverse, and descending. The large intestine is the site of a rich bacterial population and is involved in absorbing water and some electrolytes as well as in the activities involved in defecation.

BEFORE YOU GO ON . . .

1. What is the entry point for the digestive tract, and what is the role of saliva in digestion?
2. What portion of the small intestine do secretions of the liver and gallbladder enter?
3. What is the shape and design of the stomach, and what are the stomach's key segments?
4. What are the three segments of the small intestine, and what are the three ways that the surface area is enhanced?
5. What are the crypts of Lieberkühn?

► Gastrointestinal Movement, Motility, and Neural Activity

Contents are moved throughout the length of the digestive tract in a strategic and coordinated manner. Smooth muscle contractions both mix and propel digesting contents throughout the digestive tract. Digestive tract motility is largely controlled by the **enteric nervous system (ENS)**.

Smooth Muscle

The motility of substances throughout the length of the gastrointestinal tract is provided by the smooth muscle found in the wall. Longitudinal smooth muscle fibers extend along the length of the gastrointestinal tract, and the circular smooth muscle fibers wrap around the tract. Individual muscle fibers approximately 200 to 500 micrometers in length and 2 to 10 micrometers in diameter are arranged in bundles containing up to 1,000 fibers each. Adjacent bundles of smooth muscle fibers are separated by a thin region of connective tissue, but they are fused together at several points, which allows for muscle bundle contraction to occur as a syncytium. Therefore, when an action potential is fired anywhere within the muscle mass, it has the potential to be conducted throughout the muscle, thereby allowing the muscle to contract as a unit.

Contraction of the smooth muscle in the gastrointestinal tract wall appears to occur rhythmically and is associated with the presence of waves in the smooth muscle membrane potentials. Two types of electric waves occur in smooth muscle cells: slow waves and spikes. Slow waves, which it is assumed are caused by the undulating activity of $\text{Na}^+\text{-K}^+$ pumps, alter the membrane potential by 5 to 15 millivolts. Their

frequency can vary, depending largely on the location in the gastrointestinal tract. For instance, slow waves occur at a frequency of about 3 per minute in the stomach while occurring at a rate of 12 per minute in the duodenum.

Smooth Muscle Excitation

Slow waves are not actually action potentials and, therefore, do not directly evoke contraction of smooth muscle. However, when slow waves exceed -40 millivolts, they give rise to spikes, which are indeed true action potentials and thus stimulate muscle contraction. Spikes, or spike potentials, differ from the action potentials characteristic of neurons in at least two ways. First, spike potentials, which last 10 to 20 milliseconds, are about 10 to 40 times longer than neuron action potentials. Second, the ion channels involved in the spike potential are unique as well. Spike potentials appear to be caused by slow-opening and slow-closing $\text{Ca}^{2+}\text{-Na}^+$ channels, which are different from the rapidly opening and closing Na^+ channels involved in the action potentials of neurons. Spike potentials can also be distinguished from slow waves based on ion channel activity. Slow waves are not associated with an increase in intracellular calcium and, therefore, do not evoke fiber contraction. Like other muscle fibers, smooth muscle cells of the gastrointestinal tract wall contract in response to an increase in intracellular calcium concentration acting through a calmodulin-controlled mechanism.

In addition to rhythmic contraction, gut smooth muscle exhibits tonic contraction. Although demonstrating fluctuations in intensity, tonic contractions are continual and protracted, lasting as long as several minutes to hours. The origin of a tonic contraction may be the result of a repetitive series of spike potentials or the influence of certain hormones or other factors that allow for continual depolarization of the membrane potential.

► Enteric Nervous System

The gastrointestinal tract is endowed with the enteric nervous system (ENS), which is functionally distinct yet inter-connected with the central nervous system (CNS). That means that although the ENS can function on its own, its activity is still influenced by the autonomic extensions of the CNS. Furthermore, sensory neurons originating in the intestinal wall epithelium communicate with both the enteric and CNS.

The ENS extends from the esophagus to the anus, contains approximately 100,000,000 neurons, and is characterized by two main plexuses. The myenteric plexus, or Auerbach plexus, is the outer plexus and is located between the longitudinal and circular smooth muscle layers and runs the entire length of the enteric nervous system. The proximity of this complex relative to smooth muscle layers makes the myenteric plexus ideal to control motor activity along the length of the gastrointestinal tract. Stimulation of the myenteric plexus generally results in increased wall tone, rate and intensity of rhythmic contractions, and velocity of excitatory wave conduction along the wall of the gastrointestinal tract.

In contrast to those operations, stimulation of the myenteric plexus can also result in some inhibitory activity as well. For instance, some of its neurons release inhibitory neurotransmitters, such as vasoactive inhibitory polypeptide (VIP), when stimulated. The significance of this activity includes relaxation of intestinal sphincter muscles, such as the pyloric sphincter and the ileocecal valve, thus allowing passage of intestinal content from one gut segment into another. The second plexus, which is known as the submucosa plexus, or Meissner plexus, is situated within the submucosa and is mainly involved in gastrointestinal secretions and local blood flow regulation.

Neurotransmitters

Neurons of the ENS produce a variety of potential neurotransmitter substances, including acetylcholine, epinephrine, ATP, dopamine, serotonin, VIP, γ -aminobutyric acid (GABA), glycine, cholecystokinin (CCK), leu-enkephalin and met-enkephalin, substance P, secretin, neurotensin, motilin, and gastric-releasing peptide (GRP), which is the mammalian analogue of the amphibian peptide bombesin. Although the role of a few of these substances in ENS activity has been well established, the presence of other substances has not necessarily been linked to physiologic function.

Acetylcholine mediates contraction of the smooth muscle in the gut as well as secretions from the salivary glands, stomach, pancreas, and small intestine. Norepinephrine, in contrast, generally inhibits smooth contraction, secretion, and blood flow. GRP is a 27-amino acid peptide that is released from neurons in the gastric antrum and fundus, as well as the pancreas; and stimulates the release of gastrin, CCK, pancreatic polypeptide, insulin, glucagon, and somatostatin. VIP is a 28-amino acid peptide that is

produced by neurons throughout the gastrointestinal tract, salivary glands, and pancreas. VIP release causes relaxation of the LES, the proximal stomach, and the internal anal sphincter.

Sympathetic and Parasympathetic Innervation

The gastrointestinal tract is extrinsically innervated by both the sympathetic and parasympathetic systems. Both systems elicit a response in the gastrointestinal system by synapsing with neurons of the ENS first. Furthermore, chemoreceptors and mechanoreceptors in the mucosa of the gastrointestinal tract can relay afferent impulses to the CNS or elicit a reflex by way of ENS plexuses. Because the activities of the ENS and the sympathetic and parasympathetic nervous systems are not under conscious control, those systems are collectively referred to as the autonomic nervous system.

The vagus nerve supplies almost all of the parasympathetic activity down to the level of the transverse colon, whereas fibers supplied by the pelvic nerve innervate the descending colon, sigmoid colon, rectum, and the anal canal. Cholinergic fibers innervating the striated muscle in the upper third of the esophagus and external anal canal are also delivered by the vagal and pelvic nerves, respectively. Parasympathetic fibers are especially dense in the oral cavity and the most analward segments of the gastrointestinal tract, while not being particularly as dense in the small intestine. Parasympathetic stimulation generally increases gastrointestinal activity, although some inhibitory processes do result.

Contrary to parasympathetic innervation, the density of sympathetic innervation is more consistent throughout the length of the gut. Sympathetic fibers originate in the T5 through L2 regions of the spinal cord, and preganglionic fibers synapse in either the celiac, superior or inferior mesenteric, or hypogastric ganglia. From there, postganglionic fibers innervate regions of the myenteric and submucosal plexuses. Neurons of the ENS then relay signals to smooth muscle, secretory cells, and endocrine cells of the gastrointestinal tract and generally elicit a response that decreases gastrointestinal activity.

► Digestive Tract Movements

The gastrointestinal tract exhibits two basic types of movement. Propulsive movements move contents forward, whereas mixing movements allow for

a thorough blending of gastrointestinal contents. Peristalsis is the basic propulsive movement. A ring of muscular constriction encircling the gut is initiated and then begins to move forward (analward) by pushing the intestinal matter in front of the ring forward. Distention is a strong stimulus for the origin of a peristaltic wave. For instance, if intestinal matter stretches the gut wall, a contractile ring is initiated about 2 to 3 centimeters behind the point of distention, and peristalsis is propagated in the direction of the anus. In addition, the gut can relax several centimeters on the anus side of the distention to ease transit of matter into that area. Parasympathetic signals can also initiate peristalsis along with irritation of the mucosal lining of the gut. An intact myenteric plexus is necessary for effective peristaltic waves in an associated area.

Mixing movements differ from one segment of the gastrointestinal tract to another. In areas just prior to a sphincter closure, forward movement of intestinal matter is blocked and thus peristaltic waves take on a more distinctive mixing role. In other regions, local constrictive contractions occur approximately every several centimeters in a regimented fashion to help chop and blend intestinal contents.

► Gastrointestinal Vasculature

The gastrointestinal tract receives blood from several arterial branches of the abdominal aorta. For instance, the celiac artery delivers blood to the stomach, the superior mesenteric artery delivers blood to the small intestine and proximal portion of the large intestine, and the inferior mesenteric artery supplies blood to the more distal aspects of the large intestine. Small arterial branches of superior mesenteric artery ultimately serve individual villi because a capillary network is centralized inside each of those mucosal projections (see Figure 2.6).

Hepatic Portal Vein

Once blood has perfused those regions, it drains into its respective veins, which then drain into the **hepatic portal vein**. By design, blood that has perfused the gut, as well as the pancreas and spleen, is destined to flow to the liver before returning to the heart. This allows the liver to have the first shot at substances absorbed into intestinal wall capillaries. Furthermore, as the blood courses through hepatic sinusoids, gut-derived bacteria and other debris can be removed by reticuloendothelial cells before entering the circulation at large.

BEFORE YOU GO ON . . .

1. What type of muscle is found in the wall of the digestive tract and how is it arranged?
2. How do substances move through the digestive tract, and how are they mixed with digestive juices?
3. What is the nervous system of the digestive tract, and how does it interact with the CNS?
4. What is the special function of the vagus nerve?
5. What are the special features of circulation serving the gastrointestinal system?

► Gastrointestinal Endocrine and Paracrine Substances

Distributed throughout the gastrointestinal tract are cells possessing endocrine or paracrine functions or both. Those cells manufacture and secrete substances such as serotonin, cholecystokinin, gastrin, secretin, gastric inhibitory polypeptide (GIP), motilin, neurotensin, and somatostatin. Interestingly, many of those substances are also found in the neural end of the enteric nervous system.

Gastrin

Gastrin is secreted by gastrin cells (G cells), which are located primarily in the glands of the gastric antrum and also in the mucosa of the duodenum. Several polypeptides of varying lengths possess gastrin activity. All of those polypeptides possess an identical carboxyl (COOH) terminal amino acid sequence (Try-Met-Asp-Phe-NH₂), with the terminal phenylalanine (Phe) residue being aminated (NH₂). The most abundant forms are G-17 (I and II) and G-34 (big gastrin), with the number denoting the quantity of amino acids in the polypeptide. **FIGURE 2.7** presents the amino acid sequence of G-17. G-14 (minigastrin) is also physiologically active, whereas pentagastrin (G-5) is a synthetic form of gastrin. During interdigestive periods or fasting, gastrin levels in the plasma are on the order of 50 to 100 picograms per milliliter and are mostly attributable to G-34. However, when G cells are stimulated during a meal, more G-17 is released. G-17 and G-34 are equipotent; however, the half-life of G-34 is approximately 38 minutes, whereas the half-life of G-17 is only 7 minutes.

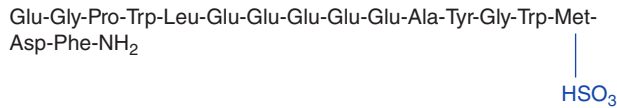
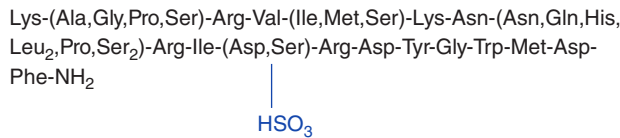
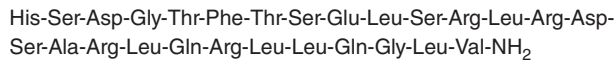
Gastrin (G-17)**Cholecystokinin****Secretin**

FIGURE 2.7 Amino Acid Composition of Gastrin, Cholecystokinin, and Secretin. Major amino acid composition of polypeptides that initiate digestion. Gastrin and cholecystokinin have polypeptides that vary in length, with this figure illustrating the “parent” compounds. Secretin is present with only one form of the polypeptide.

The stimulus for gastrin release from G cells includes the presence of small peptides, certain amino acids (especially phenylalanine and tryptophan), and calcium in the lumen of the stomach. Neural stimulation, either mediated directly by the vagus or indirectly by gastric distention-initiated ENS reflexes, also evokes gastrin release. Gastrin-releasing peptide (GRP) appears to be the neurotransmitter released as a result of vagal stimulation. The primary role of gastrin is to regulate gastric acid secretion while also mediating pepsinogen and intrinsic factor secretion. Gastrin is approximately 1500 times more potent than histamine in stimulating acid release from oxyntic glands. Gastrin also stimulates the growth of the oxyntic glands. Gastrin release is reduced relative to increasing acidity in the lumen of the stomach.

Cholecystokinin

Similar to gastrin, the polypeptide cholecystokinin (see Figure 2.7) is also present in multiple forms and is secreted from cells located in the mucosa of the duodenum and jejunum. Molecules exhibiting CCK activity have the same active COOH-terminal tetrapeptide sequence as gastrin. Isolated forms of CCK include CCK-58, CCK-39, CCK-33, CCK-22, and CCK-8. CCK release is stimulated by the presence of intraluminal fatty acids having a chain length of nine or more carbons and their corresponding monoglycerides. Partially digested proteins and individual amino acids such as phenylalanine and tryptophan, as well as intraluminal glucose, promote CCK release. GRP

also seems to stimulate the release of CCK. Among the well-established roles of CCK are to stimulate the release of pancreatic enzyme secretion, gallbladder contraction, and relaxation of the sphincter of Oddi. CCK also has an effect on gastric and intestinal motility and a trophic effect on the pancreas.

Secretin

In contrast to gastrin and CCK, secretin only has one circulating form, a 27-amino acid polypeptide (see Figure 2.7). It is released from secretin-containing cells located in the mucosa of the duodenum and jejunum when the hydrogen ion content of the proximal small intestine increases. Circulating levels of secretin increase when intraluminal pH falls below 4.5. Intraluminal fatty acids may also evoke the release of secretin. The major function of secretin is to stimulate the pancreas to release a bicarbonate-rich alkaline solution into the pancreatic duct. Secretin also promotes water and bicarbonate secretion from the biliary system. Secretin exhibits other functions as well, such as inhibition of gastric emptying, inhibition of gastric acid secretion, and the release of pepsinogen in the stomach. However, whether those functions are physiologically significant remains uncertain.

Somatostatin

Beyond mucosa cells throughout the intestinal tract, somatostatin is also manufactured and released from D cells in the pancreatic islets of Langerhans as well as nerve fibers in both the central and enteric nervous systems. Somatostatin occurs as either SS-14 or SS-28, and circulatory levels are increased due to the presence of fat and protein in the intestines and to some degree by an acidic pH in the antrum region of the stomach, as well as in the duodenum. Although it has many functions outside of digestive physiology, somatostatin is involved in the inhibition of gastrin release from G cells, in pancreatic enzyme release, and in the secretion of stomach acid. Beyond those roles, somatostatin is involved in inhibiting the release of secretin, motilin, and CCK, as well as inhibiting the absorption of amino acids, water, and electrolytes and gut motility.

Gastric Inhibitory Polypeptide

Gastric inhibitory peptide (GIP) is produced and released from cells located primarily in the duodenum and jejunum. GIP is a 42-amino acid polypeptide released in response to an intraluminal presence of several substances, including glucose, amino acids,

and hydrolyzed triglycerides, as well as being released in response to an increase in duodenal hydrogen ion concentration. Although its name suggests a regulatory role in gastric acid secretion, this function has not been proven to be physiologic. However, GIP does have a physiologic role in intensifying the glucose-stimulated release of insulin. Because of this

role, GIP is also called glucose-dependent insulinotropic peptide, thus retaining the GIP abbreviation.

Motilin

Motilin, a 22-amino acid linear polypeptide, is released from mucosal cells of the upper small intestine. The

SPECIAL FEATURE 2.1

Gastroesophageal Reflux Disease (GERD)

A growing medical problem is gastroesophageal reflux disease, commonly referred to as GERD. GERD occurs when there is reflux of acidic stomach contents back into the esophagus. This will cause heartburn and can also result in contents refluxing to the back of the throat, which leaves it sore. Without treatment, ulceration of the esophageal lining can occur. Difficulty in swallowing will result if the esophagus narrows as a result of chronic irritation. GERD may also lead to a precancerous condition known as Barrett syndrome. Regurgitation of food is not uncommon with GERD. Symptoms of GERD are more likely to occur during the night, but they may occur at other times.

GERD occurs when the lower esophageal sphincter muscle does not close properly due to a decreased tone. Under normal situations, the sphincter muscle opens upon swallowing and then closes after the food contents enter the stomach. Risk factors associated with GERD include:

- Obesity
- Alcohol intake
- Hiatal hernia
- Pregnancy
- Smoking

Medications can also lead to the development of GERD or worsen the condition and symptoms. Medications that can cause or worsen GERD include tricyclic antidepressants, asthmatic bronchodilators, dopamine-related drugs used to treat Parkinson's disease, and β -blockers used to treat heart disease.

Although certain food types can modulate the symptoms, lifestyle modifications may alleviate them. In addition to decreasing alcohol intake, people with GERD should stop smoking and lose weight. It may also be helpful to not lay down for 2 to 3 hours after consuming a meal. Eating dinner and then laying down to watch television will only exacerbate the symptoms. Sitting up following a meal will allow the food contents to be digested more effectively in the stomach first followed by further digestion when the partially digested food enters the duodenum. Snacks before bedtime, especially those that are high in fat, also increase the likelihood of GERD.

Certain foods tend to be more problematic than others. The best way for a person to determine which foods are causing a problem is to keep a food diary and then determine if GERD episodes occur after eating certain foods. In general, spicy foods tend to be more problematic. Acidic foods, such as tomatoes and citrus beverages, may need to be avoided prior to bedtime. Onion and garlic may also cause GERD episodes. Chocolate and certain oils, such as spearmint oil, are contraindicated because those tend to lessen the lower esophageal sphincter pressure. Coffee and fatty foods may also lessen the sphincter pressure. Generally speaking, foods that are good sources of protein will increase the lower esophageal pressure and are recommended. Also, small, more frequent meals are another dietary recommendation to decrease the incidence of reflux.

Many health professionals recommend use of antacids to help alleviate the symptoms of GERD. Both over-the-counter and prescription antacid medications are available. Many antacids are salts of calcium, magnesium, or aluminum with hydroxyl or bicarbonate groups to help neutralize the acids. Another class of medications used to treat GERD is the proton pump inhibitors, which include Prilosec, Prevacid, Protonix, Aciphex, and Nexium, which are available by prescription. Prilosec is also available over the counter in lower dosage forms. H_2 blockers are another class of medications. H_2 blockers include Tagamet, which has a long track record in treating GERD; Pepcid AC proton pump inhibitors appear more effective than H_2 blockers, and almost all individuals with GERD will have favorable responses.

If lifestyle modifications and medications are unable to relieve GERD, surgical intervention is required. Surgical techniques can be used to strengthen the sphincter muscle. In one technique, burning the lower esophageal sphincter results in the production of scar tissue that can strengthen the muscle.

level of motilin increases during interdigestive periods. Motilin is believed to initiate migrating myoelectric complexes (MMCs) in the duodenum, which occur every 90 minutes or so during interdigestive periods and function as a sweeping mechanism moving digestive residue analward. Motilin also stimulates the production of pepsin. Often, motilin is referred to as the “housekeeper of the gut” because it supports peristalsis in the small intestine, thereby clearing this space for the next meal.

Peptide YY

Peptide YY (or PYY) is a 36-amino acid protein produced and released by cells in the ileum and colon in response to a meal and appears to reduce appetite. In addition, a structurally similar version is produced and released by the pancreas in response to feeding. PYY works by binding to neuropeptide Y (NPY) receptors located in the autonomic nervous system (ANS) and the brain. PYY inhibits gastric motility and, therefore, functions to slow the transit of contents through the small intestine to increase the efficiency of digestion and nutrient absorption. In addition, PYY increases water and electrolyte absorption in the colon and may also suppress pancreatic secretion.

Histamine

Histamine is derived from the amino acid histidine by the actions of histidine decarboxylase. In addition to its established activities as a neurotransmitter, histamine is secreted from gastric mast cells. Although the mechanisms leading to the release of histamine from those cells are relatively unclear, the paracrine function of histamine in evoking gastric acid secretion is well known. Therapeutically, histamine H₂-receptor antagonists, such as cimetidine, inhibit parietal cell hydrochloric acid secretion as stimulated by gastrin, acetylcholine, and histamine analogues.

BEFORE YOU GO ON . . .

1. What is gastrin? How is it released and is there more than one form?
2. Where is secretin released, and what is its role in digestion?
3. What are the principal stimulants of CCK, and what is the function of this hormone?
4. What role do GIP, motilin, and PYY play in digestion?
5. What role does histamine play, and where and how is it released?

SPECIAL FEATURE 2.2

Mediators of Appetite

Hormonal Influences

Insulin

Barring anomaly, the level of circulating insulin appears to be proportionate to the volume of adipose tissue. In addition to insulin's effect on energy substrate metabolism, it also influences appetite and food intake. Insulin is able to cross the blood–brain barrier by way of a saturable transport system and may reduce feeding by inhibiting the expression of neuropeptide Y (NPY), enhancing the effects of cholecystokinin (CCK), and inhibiting neuronal norepinephrine reuptake. Thus, teleologically, the correlation between adiposity and plasma insulin levels may be an adaptive mechanism to support decreased caloric consumption. Interestingly, the influence of insulin on NPY expression is not seen in the genetically obese Zucker (*fa/fa*) rats. Because the *fa* gene codes for the leptin receptor, it is likely that some of the effects of insulin on reducing appetite are leptin mediated.

Cholecystokinin

As discussed previously, cholecystokinin is secreted by mucosal cells of the proximal small intestine in response to the presence of food components. Postprandial circulating CCK levels are related to satiety and feeding in humans. There appear to be two types of CCK receptors (A and B), and both may be involved in regulating food intake. CCK-A receptors are present within the gastrointestinal system, whereas CCK-B receptors are present in the brain.

By way of interaction with CCK-A receptors in the pylorus, CCK promotes contraction of the pyloric sphincter, which increases gastric distention. This initiates vagal afferents from the stomach that terminate in the nucleus of the solitary

(continues)

SPECIAL FEATURE 2.2 (continued)

tract within the brain stem. Impulses are then transmitted to the parabrachial nucleus, which is then connected to the ventromedial hypothalamus, resulting in decreased food intake. This mechanism is diminished by experimental vagotomy.

Although CCK-B receptors are found in the brain, CCK circulating in the systemic circulation does not cross the blood-brain barrier. Therefore, it has been suggested that because the brain also produces some CCK, afferent neural signals may result in the release of CCK in the cerebral spinal fluid, which binds with CCK-B receptors and decreases feeding.

Neuroendocrine Influences

Leptin

In 1995, leptin, a protein chain of 167 amino acids, was discovered as a product of the obese (*ob*) gene. Its receptor was cloned shortly thereafter. The name *leptin* is derived from the Greek word *leptos*, meaning “thin.” In obese hyperphagic, homozygote *ob/ob* mice; two prominent mutations have been identified that lead either to a lack of mRNA expression or to production of an ineffective product. Leptin has been shown to reduce food intake and increase energy expenditure in both obese and lean animals. In humans, adipose cells also synthesize and secrete this protein relative to the amount of stored body fat. Leptin receptors have been found in various body tissues, such as the kidneys, liver, heart, skeletal muscle, hypothalamus, pancreas, and anterior pituitary. Leptin receptors found in the arcuate nucleus of the hypothalamus have led researchers to hypothesize that leptin may somehow regulate satiety. Leptin appears to also decrease NPY synthesis and release from that same region. In addition, leptin has been shown to increase corticotropin-releasing factor (CRF) expression and release from the hypothalamus.

It is possible that serum leptin levels are elevated in some obese subjects due to the receptor’s resistance to leptin’s action. This is supported by another model of genetic **obesity** in mice. The so-called obese diabetic mouse has a mutation in the diabetes (*db*) gene. It is typical for those mice to have a 10-fold greater level of leptin in comparison with lean control mice. Because it has not been determined that there is an anomaly in the *ob* gene in these animals, a defect in the receptor is suspected at present. Some human cross-sectional studies have revealed that obese individuals may also have elevated levels of leptin; however, it is not clear whether there is a defect in the hypothalamic leptin receptor in these individuals. Thus, it has been speculated that there may be leptin resistance.

The presence of receptors in the pancreas has also led researchers to hypothesize that serum leptin may somehow regulate insulin metabolism. Whether this is indeed the case is unresolved. In vitro studies have demonstrated that leptin does not alter the uptake of glucose in the absence of insulin, nor does it influence glucose’s sensitivity to insulin. Other studies appear to strongly correlate a counter-regulatory effect of leptin with insulin resistance.

Leptin may also play a role in energy substrate metabolism, because there may very well be an inverse correlation between leptin and energy intake, fat intake, resting energy expenditure, carbohydrate oxidation, and **respiratory exchange ratio (RER)**. Therefore, those resistant to leptin may encounter two metabolic obstacles: (1) the link between the central nervous system and appetite regulation is disturbed, and (2) resting energy expenditure is decreased, facilitating weight gain. Also, there is evidence to suggest that leptin levels decrease in response to weight loss and remain decreased as long as the weight loss is maintained. Furthermore, increased levels of leptin have been found in normal-weight and obese women compared with their male counterparts, as well as in female-patterned obesity (or peripheral fat stores). This is an expected finding because females have a greater percentage of body fat mass than males.

Ghrelin

Ghrelin is a hunger-stimulating hormone; its level increases before meals and decreases after meals. Ghrelin is produced by P/D1 cells lining the fundus of the stomach and epsilon cells of the pancreas and is considered the counterpart of leptin. In addition, ghrelin is produced in the hypothalamus and acts to stimulate the secretion of growth hormone from the anterior pituitary gland. In fact, much of ghrelin’s ability to increase hunger is based on its interaction with the hypothalamus by activating NPY neurons in the arcuate nucleus. Both leptin and insulin influence the sensitivity of those neurons to ghrelin. Furthermore, ghrelin also plays a role in the mesolimbic cholinergic-dopaminergic system, which communicates “reward” in the presence of food as well as alcohol.

Neuropeptide Y

Neuropeptide Y is a peptide synthesized and secreted by the neurons of the arcuate nucleus of the hypothalamus, partially in response to leptin binding to its receptors. Increased activity of those neurons has been demonstrated

in animal studies during periods of energy deficit, and; therefore, obesity may develop in response to abnormally increased production. NPY appears to stimulate food intake, especially carbohydrate sources. The paraventricular nucleus appears to be particularly sensitive to NPY. Interestingly, NPY is also synthesized and released by the adrenal gland and sympathetic nerves into circulation; however, it does not cross the blood–brain barrier.

When NPY is injected directly into the medial hypothalamus of satiated animals, feeding is stimulated. Furthermore, there is a preference for carbohydrates. NPY seems to increase the percentage of carbohydrate used for energy while simultaneously being associated with a reduction in energy expenditure. It is believed that the NPY-induced, increased use of carbohydrate allows for the production of more acetyl CoA for lipogenesis. NPY also seems to support fat storage in white adipose tissue, while decreasing brown adipose tissue activity. Interestingly, NPY may have a stimulatory effect on the secretion of insulin, vasopressin, and leuteinizing hormone.

Peptide YY

Peptide YY is related to NPY. Peptide YY is a 36 amino acid peptide produced by cells of the ileum and colon. Upon feeding, the level of this peptide increases 15 minutes after a meal. When the peptide is administered from an exogenous source, its major effect is to inhibit energy intake as well as body weight in both rodent models and humans. Apparently, a possible mechanism by which this functions is to block the effect of NPY neurons while binding to other neurons to signal satiety.

Galanin

Galanin is another peptide factor that, along with its receptors, is found in greater concentrations in the hypothalamus. Animal studies suggest that galanin increases feeding as well as the preference for carbohydrate and fat. In addition, galanin is associated with a reduction in energy expenditure because it inhibits sympathetic nervous system activity; however, it does not seem to influence the proportion of fuel used (e.g., carbohydrate vs fat). Two subclasses of receptors have been identified in rats but only one in humans. Unlike leptin and NPY, plasma galanin concentrations and activity do not appear to be regulated by weight. Galanin also has an inhibitory effect on insulin secretion, and synthesis of galanin is inhibited in response to increased serum insulin.

► Digestion and Absorption

The foundation of human nourishment is the consumption of other living entities or their products to obtain elements and molecules common to both. Essential nutrients are substances that humans are unable to produce, either at all or in adequate quantities, and thus must be provided by the diet. Because of the complex integration of nutrients into their sources, digestive activities are necessary to liberate nutrients, such as freeing minerals from proteins; to reduce the size of nutrients, such as breaking down complex proteins to amino acids or complex **starch** to monosaccharides; and to modify nutrients so that they can be recognized by transport systems involved in their absorption.

Phases of Digestion

Digestive operations are influenced by several factors. For instance, the mere thought or smell of food can initiate activities in the digestive tract. In addition, many physical and chemical interactions modify digestive activities. Based on this, digestion can be separated into three phases:

1. *Cephalic phase.* The cephalic phase occurs when food stimulates pressure-sensitive mechanoreceptors in the mouth and chemoreceptors in the mouth and nasal cavity. The mere thought of food can also trigger central pathways that relay impulses to vagal efferent nerves that reach the stomach. Thus, the cephalic phase can be blocked by vagotomy.
2. *Gastric phase.* The gastric phase begins when distention of the stomach wall stimulates mechanoreceptors. This action elicits vagovagal and intramural reflexes that stimulate the release of gastrin and other hormones, thereby increasing stomach secretions as well as intestinal secretions.
3. *Intestinal phase.* The intestinal phase occurs as a result of both mechanical and chemical events. Duodenal luminal distention leads to the release of a hormone called entero-oxyntin. Meanwhile, interaction between nutrients and receptors elicits the release of other hormones, such as CCK and secretin.

Oral Cavity

Once food enters the mouth, it is chewed (masticated) and bathed in salivary juice. Incisors are anterior in the mouth and provide a strong cutting action, whereas the more posterior molars provide a grinding mechanism. **FIGURE 2.8** shows the structure of a tooth. Chewing is controlled by nuclei in the brain stem, which innervates the muscles of the jaw via the fifth cranial nerve. A coordinated effort by all muscles in the jaw can generate a force of 55 pounds on the incisors and 200 pounds on the molars. Chewing physically tears food apart while actions of the tongue help position food between the teeth; the combination of actions mixes food with saliva.

Saliva

Saliva lubricates food for easier swallowing, solubilizes food components for taste perception, cleans the mouth and teeth to prevent caries, and initiates chemical digestion. Approximately 1 to 1.5 liters of saliva are produced daily by the glands of the oral cavity. The parotid, submandibular, and sublingual glands, along with well-distributed buccal glands, are the principal glands involved in producing a complex compilation of enzymes, mucus, R proteins, growth factors, antibacterial and antiviral factors, ions, and water (see Figure 2.3). Finally, saliva contains the blood group substances A, B, AB, and O.

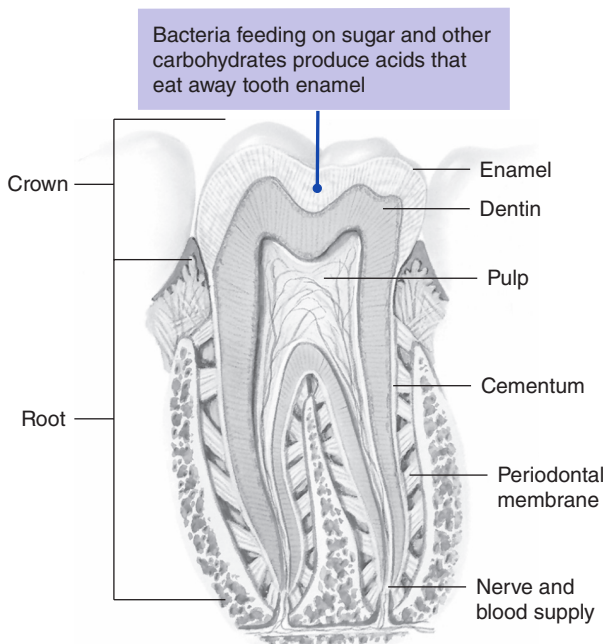


FIGURE 2.8 General Anatomy of a Tooth. Poor nutrition may compromise the integrity of teeth. The enamel portion is susceptible to erosion by bacteria feeding on sticky carbohydrates. Enamel erosion allows other structures to be compromised, leading to dental caries.

Saliva Proteins: Enzymes and Mucus

Two types of protein secretions are found in saliva: serous and mucous. The serous type of protein secretion, which is secreted by the parotid, submandibular, and sublingual glands; contains ptyalin (**α -amylase**) and lingual lipase and is also secreted by the sublingual glands. α -Amylase begins the chemical digestion of starches by cleaving α 1-4 links between glucose monomers. Lingual lipase hydrolyzes certain ester bonds of triglycerides and is of particular significance in infants. Another salivary enzyme, kallikrein, does not have catabolic properties but supports the digestive process by converting a plasma protein into bradykinin, which increases blood flow to salivary glands. The mucous type of protein secretion contains the lubricating glycoprotein mucin. Along with the submandibular and sublingual glands, the buccal glands also secrete mucus.

Saliva Electrolytes

The inorganic component of saliva includes sodium, potassium, chloride, bicarbonate, calcium, magnesium, and phosphate. At rest, saliva is hypotonic; however, the potassium concentration (30 milliequivalents per liter [mEq/L]) is greater than plasma levels. In contrast, the concentrations of sodium, chloride, and bicarbonate, all about 15 mEq/L, are below plasma levels. The concentrations of sodium and chloride in saliva at rest may be only about 10 to 15% of their levels in plasma. When saliva flow is stimulated, the concentration of potassium decreases, although not below plasma levels. In contrast, the concentrations of sodium, chloride, and bicarbonate increase, with the latter rising above plasma concentration. This increases salivary pH to approximately 7.8 from a resting pH of between 6.0 and 7.0.

Saliva is very important for oral hygiene. With the exception of periods of sleep, saliva is secreted at a basal rate of about 0.5 milliliter per minute, with the protein being predominantly of the mucous type. The secretion of saliva helps wash away pathogenic bacteria and residual food particles from teeth. Saliva also contains antibacterial factors such as thiocyanate ions, several proteolytic enzymes (including lysozyme), and antibodies, which collectively destroy a significant quantity of bacteria in the oral cavity.

Although the concentration of sodium and potassium can be influenced by aldosterone and antidiuretic hormone, the rate of salivary flow is controlled autonomically. That is to say that hormones that influence the release of other digestive secretions have little effect on salivary flow. Furthermore,

the autonomic control of salivary secretion is different from many other organs in that both parasympathetic and sympathetic activity will elicit flow. However, parasympathetic activity has a far greater influence on flow.

Esophagus

The act of swallowing involves both voluntary and involuntary activity. Three overlapping layers of striated muscle—the superior, middle, and inferior pharyngeal constrictors—make up the muscular wall of the pharynx. The inferior constrictor also thickens at a point to form a muscular ring that constitutes the upper esophageal sphincter. The striated muscle continues down about one-third of the length of the esophagus and gives way to circular and longitudinal smooth muscle. Circular smooth muscle thickens at the distal aspect of the esophagus, forming the lower esophageal sphincter.

The act of swallowing is complex and involves coordinated and unvarying efforts of both voluntary and involuntary actions. At rest, the upper esophageal sphincter is contracted to close the esophageal inlet. In contrast, the pharyngeal muscle exhibits only a low level of tone. The act of swallowing involves a series of voluntary and even some involuntary motions occurring in sequence, beginning with the clenching down of the jaws. Subsequently, the tongue is elevated against the hard palate, and elevation of the soft palate allows the nasopharynx to separate from the oropharynx. Next, there is a voluntary and then an involuntary contraction of the pharyngeal muscles that moves in the direction of the esophageal inlet. Concomitantly, strap muscles in the neck move the pharyngoesophageal junction, thereby properly aligning the esophageal inlet with the pharynx. The 1- to 2-second relaxation of the upper esophageal sphincter allows the bolus of food to pass into the esophagus after being forced through the mouth by the tongue and through the pharynx by its peristaltic contraction.

Esophageal Sphincter

A powerful contraction of the upper esophageal sphincter is associated with the initiation of a peristaltic wave that propels food along the length of the esophagus. There is no delay in the transition from striated muscle to smooth muscle contraction, and a bolus of food can smoothly traverse the length of the esophagus in about 6 to 9 seconds. Relaxation of the lower esophageal sphincter occurs as the peristaltic wave is initiated and propagates to the length of

the esophagus. It remains relaxed until the peristaltic wave meets the sphincter; then, after a brief interlude to allow the bolus to move into the stomach, it contracts forcefully.

Stomach

The primary operations of the stomach are to provide a depot for ingested food and to regulate its release into the small intestine; provide an acidic environment supportive of protein digestion and bacteriocidal activities; secrete a proteolytic enzyme; and secrete substances that assist in vitamin B₁₂ absorption.

The outer longitudinal, middle circular, and inner oblique layers of smooth muscle in the wall of the stomach can relax and allow for the accommodation of approximately 1.5 liters of content without significantly increasing intragastric pressure. Furthermore, the musculature of the stomach wall provides both mixing movements as well as the propulsive movements that allow for a regulated release of gastric contents into the small intestine. Those layers (see Figure 2.4) can differ from one another with regard to distribution throughout the stomach as well as in their thickness in different regions of the stomach. For instance, whereas the circular layer is for the most part found completely throughout the stomach wall, the longitudinal layer is absent from the anterior and posterior surfaces. Also, the thickness of both the circular and longitudinal layers increases in a proximal to distal manner in the stomach.

Glands located largely in the body and fundus contain a variety of exocrine cell types. Those include parietal (oxyntic) cells, which secrete HCl and intrinsic factor; peptic cells, which secrete mainly pepsinogen; and mucous neck and surface cells, which produce large amounts of mucus (see Figure 2.5). Some endocrine cells can also be found lining the oxyntic gland. Quantitatively, parietal cells make up approximately one-third of the cells lining the gland; gastric chief cells make up about 20 to 25%; and mucous neck and surface cells make up about 20 and 10%, respectively.

The general release of gastric secretions is primarily under the control of acetylcholine, gastrin, and histamine, all of which perform their function by first binding with their respective receptors on secretory cells. Acetylcholine stimulates the release of secretions from all gastric secretory cell types. This includes pepsinogen from peptic cells, HCl from parietal cells, mucus from mucous neck cells, and gastrin from G cells. In contrast, gastrin and histamine strongly stimulate the release of HCl from parietal cells but have little stimulatory impact on other secretory cell types.

Gastric Juice and Hydrochloric Acid

Hydrochloric acid, which has a pH of 0.8, is released by parietal cells and creates an acidic environment in the stomach. The pH of stomach juice is approximately 1.5 to 2.5, which is important for (1) denaturing complex three-dimensional proteins, (2) activating pepsin, (3) liberating various nutrients from organic complexes, and (4) destroying ingested microbes. The mixture of ingested material and gastric secretions is known as chyme.

During interdigestive periods, basal acid secretion is approximately 10% of maximum and exhibits a circadian rhythm, with the output during the evening being significantly higher than that in the morning. The stimulation of gastric acid release in response to a meal is divided into three phases. The cephalic phase accounts for approximately 30% of gastric acid secretion, and the gastric and intestinal phases produce 60 and 10% of gastric acid secretion, respectively. Vagal innervation can increase gastric acid secretion directly by stimulating parietal cells via acetylcholine as well as indirectly by stimulating the release of gastrin via GRP. The cephalic phase release of gastric acid can be inhibited by low stomach pH. Because the pH of gastric acid secretion is about 2.0, acid release is impeded until food proteins reach the stomach and buffer the acid, thus causing the pH to climb above 3.0. This allows the cephalic phase to have its most significant impact on gastric acid secretion.

The gastric phase begins when distention of the stomach wall stimulates mechanoreceptors. This action elicits vagovagal and intramural reflexes that stimulate both gastrin release and acid secretion. The vagovagal reflex stimulates acid secretion by the same means as the cephalic phase. Furthermore, distention of the mucosa around oxyntic glands increases acid release by a local reflex mechanism. As mentioned previously, the release of gastrin is inhibited by a low gastric intraluminal pH; however, without regard to intraluminal pH, distention will still result in acid release by reflex and local mechanisms. Meanwhile, the intestinal phase of gastric acid secretion is relatively minor and not exactly clear. Duodenal luminal distention increases acid secretion by way of a hormone named entero-oxyntin. Furthermore, the uptake of amino acids into duodenal mucosal cells appears to be associated with increased acid release.

Pepsin

Pepsin is an endopeptidase and is manufactured and stored in an inactive pepsinogen proenzyme or zymogen form that has a molecular weight of approximately 42,500 daltons. There are two primary pepsinogen

molecules, denoted as I and II. A third class of pepsinogen, called slow-moving protease because of its slow migration rate in an electrophoretic field, has also been identified. Pepsinogens are converted to active pepsins at a low pH by the loss of a portion of their NH₂-terminus amino acid sequence. They then function optimally at a pH below 3.5 and hydrolyze interior peptide bonds, especially those involving aromatic amino acids. The α -amylase derived from salivary secretions continues to digest complex carbohydrates in the stomach; however, it becomes inactivated in the highly acidic environment.

Intrinsic Factor

Intrinsic factor, which is a mucoprotein with a molecular weight of 55,000 daltons, is required for efficient absorption of vitamin B₁₂ in the small intestine. Once vitamin B₁₂ is released from polypeptides in foods (via gastric pepsin), it can combine with intrinsic factor. However, most of the vitamin B₁₂ in the stomach will initially combine with R proteins because it has a greater affinity for R proteins. R Proteins are also secreted by gastric glands. The “R” denotes the rapid transit of those proteins in an electrophoretic field.

Gastric Emptying

Gastric emptying occurs as a result of intense peristaltic contractions in the antrum. For the most part, antral peristaltic contractions are weak and function as a mixing mechanism for food and gastric secretions. However, approximately 20% of the time when food is present, the peristaltic waves are about six times more intense than mixing waves, and the constricting rings propel food powerfully toward the pylorus. Each intense wave forces or pumps about 1 to 3 milliliters of chyme into the duodenum.

Release of gastric contents into the small intestine occurs intermittently and is regulated by several stimulatory and inhibitory factors that originate in both the stomach and small intestine. The degree of filling and the excitatory effect of gastrin on gastric peristalsis compete with duodenal signals such as enterogastric feedback reflexes and hormonal feedback. Generally, the greater the gastric distention, the more rapid the emptying. Furthermore, liquids seem to be emptied more rapidly than solids. Perhaps, the most rapidly emptied substance is an isotonic saline solution. Its emptying rate decreases as the solution is modified to a more hypotonic or hypertonic concentration. The presence of fat substances in the duodenum slows gastric emptying by stimulating the release of CCK, which inhibits

emptying. Acid in the duodenum also decreases gastric emptying by a neural reflex mechanism.

Small Intestine

In the small intestine, chyme is mixed with pancreatic secretions and bile by way of segmentation or mixing contractions of circular smooth muscle and sleeve contractions of longitudinal smooth muscle. Meanwhile, peristaltic waves serve to propel food analward through the small intestine. The low pH of entering chyme is quickly neutralized by bicarbonate and H₂O secretions of both the pancreas as well as the Brunner glands, which are located in the mucosa of the first few centimeters of the duodenum. Cells in the crypts of Lieberkühn secrete approximately 1800 milliliters of fluid per day. The composition of this fluid is similar to extracellular fluid, with a slightly alkaline pH. The fluid provides a medium for nutrient absorption and is subsequently reabsorbed by enterocytes. Those cells are particularly sensitive to toxins such as those produced by *Vibrio cholerae*. Once small water-soluble substances, such as amino acids, monosaccharides, and certain vitamins and minerals, traverse the enterocyte lining, they can enter the circulation by entering the capillary within the center of the villus.

Pancreatic Digestive Juice

Pancreatic acini and associated duct cells secrete a juice that is clear, colorless, alkaline, and isotonic. It contains both organic and inorganic components, which ultimately reach the duodenum via the pancreatic duct and subsequently the common bile duct. Total pancreatic juice secretion for an adult is approximately 1 to 2 liters daily.

Protein, mostly in the form of enzymes, is a main component of pancreatic digestive juice (**TABLE 2.1**).

Digestive enzymes are produced and stored as inactive zymogen molecules to prevent autolysis of acini cells. Activation of digestive zymogen enzymes takes place in the duodenum and is initiated by the brush border enzyme enterokinase (enteropeptidase). Enterokinase activates trypsinogen by cleaving an NH₂-terminal portion of the molecule. Trypsin, the active form of trypsinogen, is then able to activate other digestive zymogens, including trypsinogen. Meanwhile, trypsin inhibitor and colipase are not necessarily digestive enzymes. Trypsin inhibitor appears to be active in pancreatic acini secretory vesicles. Its purpose is to protect pancreatic parenchyma by binding to trypsin molecules formed in premature autocatalysis. Procolipase, once activated, is a cofactor for lipase activity. In addition, other proteins, such as immunoglobulins, kallikrein, lysosomal enzymes, alkaline phosphatase, and albumin, are part of pancreatic secretions, although in relatively small quantities.

Pancreatic secretions include an inorganic component composed of water, sodium, potassium, chloride, calcium, and magnesium, plus bicarbonate (HCO₃⁻). Calcium and magnesium are present in concentrations approximating 25 to 35% of their plasma concentrations. The large production of bicarbonate in ductal epithelium is attributed to intracellular conversion of CO₂ and H₂O via the enzyme carbonic anhydrase. The release of bicarbonate into the duct lumen uses a HCO₃⁻/Cl⁻ antiport mechanism.

Pancreatic Juice Delivery

Basal secretion of the aqueous component of pancreatic juice, which is largely H₂O and bicarbonate, is about 2 to 3% of the maximal rate, whereas the basal secretion of the enzymatic component is approximately 10 to 15% of maximal. Although the mechanisms responsible for basal secretions are

TABLE 2.1 Pancreatic Digestive Enzymes

Proteolytic	Lipolytic	Amylolytic	Nucleases	Others
Trypsinogen	Lipase	α-Amylase	Deoxyribonuclease	Procolipase
Chymotrypsinogen	Prophospholipase A ₁		Ribonuclease	Trypsin inhibitor
Proelastase	Prophospholipase A ₂			
Procarboxypeptidase A	Esterase			
Procarboxypeptidase B				

undetermined, the mechanisms involved in stimulated secretion are well understood. The release of the aqueous portion of pancreatic secretion is largely related to duodenal intraluminal pH, whereas the enzymatic component is attributed primarily to the presence of fat and protein. Therefore, stimuli are strongest during the intestinal phase of digestion; however, secretion will also occur to a lesser extent during the cephalic and gastric phases.

During the cephalic phase, vagal efferents to the pancreas release acetylcholine at both ductule and acinar cells, with a stronger response being evoked within acinar cells. The result is a relatively low volume of pancreatic juice with a relatively high concentration of enzymes. Subsequently, distention of the stomach stimulates pancreatic secretion via a vagovagal reflex. The contributions of the cephalic and gastric phases to total pancreatic juice production may be approximately 20% and between 5 and 10%, respectively.

The intestinal phase accounts for as much as 70 to 80% of pancreatic secretory response because the presence of protein and fat in an acidic chyme mixture elicits the release of secretin and CCK. In addition, products of protein and fat digestion, as well as acid, stimulate pancreatic enzyme release as they interact with duodenal wall receptors. This results in a vagovagal reflex with acetylcholine being released at the synapses with both ductule and acinar cells. Acetylcholine and CCK, both independently and combined, have little stimulatory impact on ductule cells; however, they can potentiate the effects of secretin.

The Gallbladder and Bile Storage and Release

As much as 1200 milliliters of bile is secreted by the liver daily. Bile is produced almost continually in hepatocytes, which are epithelial cells arranged in plates in liver lobules. Bile is secreted into tiny bile canaliculi (“little canals”) that run between the hepatocyte plates and drain into a series of larger ducts and then into the hepatic duct and then the common bile duct. Bile flowing through the common bile duct can then either be released into the duodenum or drain into the cystic duct.

During fasting periods, as much as half of the hepatic bile enters the gallbladder, while the remaining bile continues through to the small intestine. More than 90% of the bile acids (bile salts) emptied into the small intestine are reabsorbed in the distal ileum. Via the portal vein, they are returned to the liver and resecreted into bile, where again approximately half will

drain into the gallbladder. As fasting becomes more protracted, bile storage in the gallbladder is increased. The recirculation of bile acids is called enterohepatic circulation. A single bile acid molecule may make as many as 18 circuits before being eliminated in the feces.

Bile Composition

Bile is a watery composite of substances such as bile acids, bilirubin, cholesterol, fatty acids, phospholipids, electrolytes, and bicarbonate (TABLE 2.2). During interdigestive periods, bile is routed into the cystic duct for storage in the gallbladder. Although the maximal volume of the gallbladder is approximately 20 to 60 milliliters, the equivalent of 450 milliliters can be stored within the gallbladder due to the concentrating efforts of its wall mucosal cells. Bile is normally concentrated 5-fold; however, mucosal efforts can produce a stored bile solution that is concentrated 12- to 20-fold. Water, sodium, chloride, and other electrolytes are absorbed by the mucosal cells, thereby concentrating the remaining substances, as shown in Table 2.2. Even though bile acids and other components are concentrated in the gallbladder, the stored solution is still isotonic, and the pH is lowered.

TABLE 2.2 Concentration Differences: Hepatic and Gallbladder Bile

	Hepatic Bile ^a	Gallbladder Bile ^b
Bile salts (mEq/l)	30	300
Bilirubin (mg/100 ml)	100	1,000
Cholesterol (mg/100 ml)	100	600
Na ⁺ (mEq/l)	145	300
K ⁺ (mEq/l)	5	12
Ca ²⁺ (mEq/l)	5	23
Cl ⁻ (mEq/l)	100	10
HCO ₃ ⁻ (mEq/l)	28	10

^apH 7.4, ^bpH 6.5

Bile is important not only because it supplies several substances essential for lipid digestion but also because it provides an avenue for the elimination of some substances that are inappropriate for urinary excretion. In general, these substances are organic and relatively large (molecular weight > 300). Also, their hydrophobicity results in their binding to plasma albumin, which decreases their filtration into the renal tubular system. The most significant of those substances is bilirubin, which is a metabolite of hemoglobin produced by reticuloendothelial cells of tissue such as the spleen. Bilirubin is released into the blood and binds with albumin. Hepatocytes remove bilirubin and conjugate it to glucuronic acid, forming bilirubin glucuronide, which is then added to bile. Because cholesterol circulates within lipoprotein complexes and is not filtered by the kidneys, its presence in bile may also be interpreted as an excretory mechanism for that substance.

In addition to entering the body in foods, water forms the basis of digestive secretions. Thus, digestion occurs within a water-based medium. Bile acids act as detergents to solubilize small lipid droplets in the watery medium. With the assistance of colipase, the coating of lipid droplets with bile acids allows the interaction of pancreatic lipase and cholesterol esterase with their substrates.

Gallbladder Contraction

When stimulated, such as in the presence of a meal, the smooth muscle within the wall of the gallbladder contracts and bile is propelled toward the small intestine. The most potent stimulus for emptying of the gallbladder during intradigestive periods is CCK. The emptying of the gallbladder can also be stimulated by cholinergic nerve fibers from both the vagal nerve and the enteric nervous system. It is likely that vagal discharges actually initiate gallbladder contraction and that combined stimuli maintain gallbladder contraction during digestion. This would discourage retrograde flow of bile back into the gallbladder as well as the draining of bile coming from the liver during periods of digestion. The gallbladder releases about two-thirds of its bile within the first hour of digestion. CCK also evokes relaxation of the sphincter of Oddi, thus allowing bile to flow into the duodenum.

Digestive Enzymes of the Small Intestine

Enterocytes not only provide the entry site for nutrient absorption but they also play an integral part in nutrient digestion. Several carbohydrate-digesting enzymes, including disaccharidases (e.g., lactase,

maltase, sucrase) and α -1-6 dextrinase, as well as enterokinase, are associated with the brush border. Furthermore, proteases specific for short-chain peptides are located within enterocytes and play a significant role in finalizing protein digestion.

Small Intestine Absorption

Several transport proteins are located on the luminal surface, as well as the basolateral surfaces, of enterocytes and facilitate absorptive operations. For example, the absorption of glucose first involves a Na^+ -dependent transport system, which translocates glucose and sodium inside the enterocyte. Glucose can then cross the basolateral membrane by facilitative diffusion. Meanwhile, sodium is actively pumped across the basolateral membrane by a Na^+ - K^+ ATPase pump. The continual absorption of glucose through enterocytes is dependent on an electrochemical gradient for sodium.

In contrast, lipid-soluble substances, such as cholesterol esters, triglycerides, and lipid-soluble vitamins are primarily incorporated into chylomicron lipoproteins within enterocytes, which then enter the lacteal in the central region of the villi. The small intestine absorbs the bulk of the nutrients, while some absorption also occurs in the stomach and colon.

Large Intestine

The large intestine, or colon, engages in two primary operations. First, it absorbs water and electrolytes from the entering content, a function that occurs predominantly in the proximal half. Second, it stores fecal matter until defecation, a function that occurs in the distal half. The large intestine can absorb as much as 5 to 7 liters of fluid and electrolytes in a day, if so challenged. Despite lacking villi, the mucosa of the large intestine is amply supplied with crypts of Lieberkühn, whose cells secrete copious amounts of mucus.

The large intestine is inhabited by more than 400 different species of bacteria. Some bacteria produce nutrients that can be absorbed, including vitamin K, biotin, and short-chain fatty acids (e.g., acetic, propionic, and butyric acids). The composition of feces is approximately 30% bacteria, 10 to 20% fat, 10 to 20% inorganic matter, 2 to 3% protein, and 30% undigested fibers and dried components of digestive juices, such as bilirubin and its metabolites. The coloring of feces is primarily attributable to the presence of stercobilin and urobilin, which are metabolites of bilirubin. Meanwhile, the odorous characteristics of feces are due to the presence of bacterial by-products, such as indoles, skatole, mercaptans, and hydrogen

sulfide and are highly individualized based on diet and colonic bacterial profile.

Probiotics

The term **probiotic** literally translates as “for life” and is most commonly used to describe the bacteria in our digestive tract that are supportive of health. The digestive tract is home to trillions of bacteria, which fall into two general camps: those that promote health (probiotics) and those that seem to be problematic when it comes to optimal health. What seems to be very important is the balance between the two. Ideally, we want more of the health-promoting bacteria and less of the other type. Probiotic bacteria include lactic acid bacteria and Bifidobacteria; those are available in some food, such as dairy and soy yogurts, and as dietary supplements.

Probiotics promote optimal digestion and absorption of nutrients and promote a healthy digestive tract. Research supports the notion that regular consumption of probiotics may help with some intestinal conditions, such as irritable bowel syndrome and inflammatory bowel disease and help lower the risk of colon cancer.

What is more, the positive effects of probiotics might not be limited to the digestive tract. Research suggests that regular consumption of probiotics supports healthier blood cholesterol and blood pressure levels as well as supporting optimal immune system actions and playing a potential role in weight control.

Prebiotics

Nondigestible carbohydrates and other dietary substances that encourage the growth of beneficial bacteria (e.g., *Lactobacillus* bacteria) and decrease deleterious pathogens (e.g., *Escherichia coli*) in the gut are prebiotics. Resistant starches, oligofructose, and other oligosaccharides are examples of prebiotics. There are many products today that are sold as prebiotics in a supplement form. Besides the beneficial impact on promotion of favorable intestine microflora, the fermentation resulting from the bacteria upon the carbohydrates results in short-chain fatty acids. The short-chain fatty acids produce an environment more favorable to beneficial bacteria. Prebiotics are discussed in greater detail in Chapter 4 on health benefits of fiber and structural carbohydrates.

SPECIAL FEATURE 2.3

Bariatric Surgery

Bariatric surgery has become more frequent as a weight loss method. However, its use is restricted to the morbidly obese. Normally individuals with a BMI of 35 to 40 or greater, depending on the presence of other diseases, are good candidates for surgery. Prior to having such procedures, normally, other methods of calorie restriction and exercise should have been attempted. Lifelong changes in lifestyle are the likely outcomes of several of those procedures. There are four basic surgical procedures used: 1) gastric banding (lap-banding); 2) gastroplasty, 3) gastric sleeve, and 4) gastric bypass (Roux-En-Y) are the most common. (FIGURE 1).

With **gastric banding**, a silicon band is placed around the top portion of the stomach that leaves a small stomach pouch. The band has saline in it and this can be used to either enlarge or reduce the opening to the rest of the stomach. A pouch under the abdominal skin can have saline either injected or removed to alter the volume of the opening. The idea of having a pouch is that a feeling of fullness or satiety will be enhanced, resulting in decreased food intake. **Gastroplasty** requires that the upper portion of the stomach be stapled but leave a small opening to the distal stomach. The main difference between this procedure and gastric banding is that the opening to the distal stomach can be adjusted with the saline infusion within the silicon band. The opening to the distal stomach in gastroplasty is normally fixed in size compared with the banding technique. A variant of this surgery is the **gastric sleeve** procedure where a different portion of the stomach is stapled. Food travels from the esophagus, through the stomach or sleeve, and the small intestine.

Gastric bypass is a more involved procedure that facilitates weight loss not only on the smaller stomach size but on creating an environment for malabsorption of nutrients. A more common name for this procedure is **Roux-En-Y bypass**. Here, the upper part of the stomach is stapled and an opening is created that will feed into the small intestine, thereby eliminating food from entering the distal part of the stomach. Often, the entire duodenum is bypassed, depending on the type of bypass surgery. The procedure does result in more significant side effects. Dumping syndrome after eating is common. Micronutrients are often malabsorbed and require a lifelong monitoring of status of nutrients such as vitamin B₁₂, folic acid, potassium, magnesium, iron, and copper. Initially vomiting, rapid heartbeat, and other issues cause behavioral modification in the subject to decrease the volume of food. The pouch may increase somewhat over time as many patients tend to consume large amounts of liquid instead of solid food.

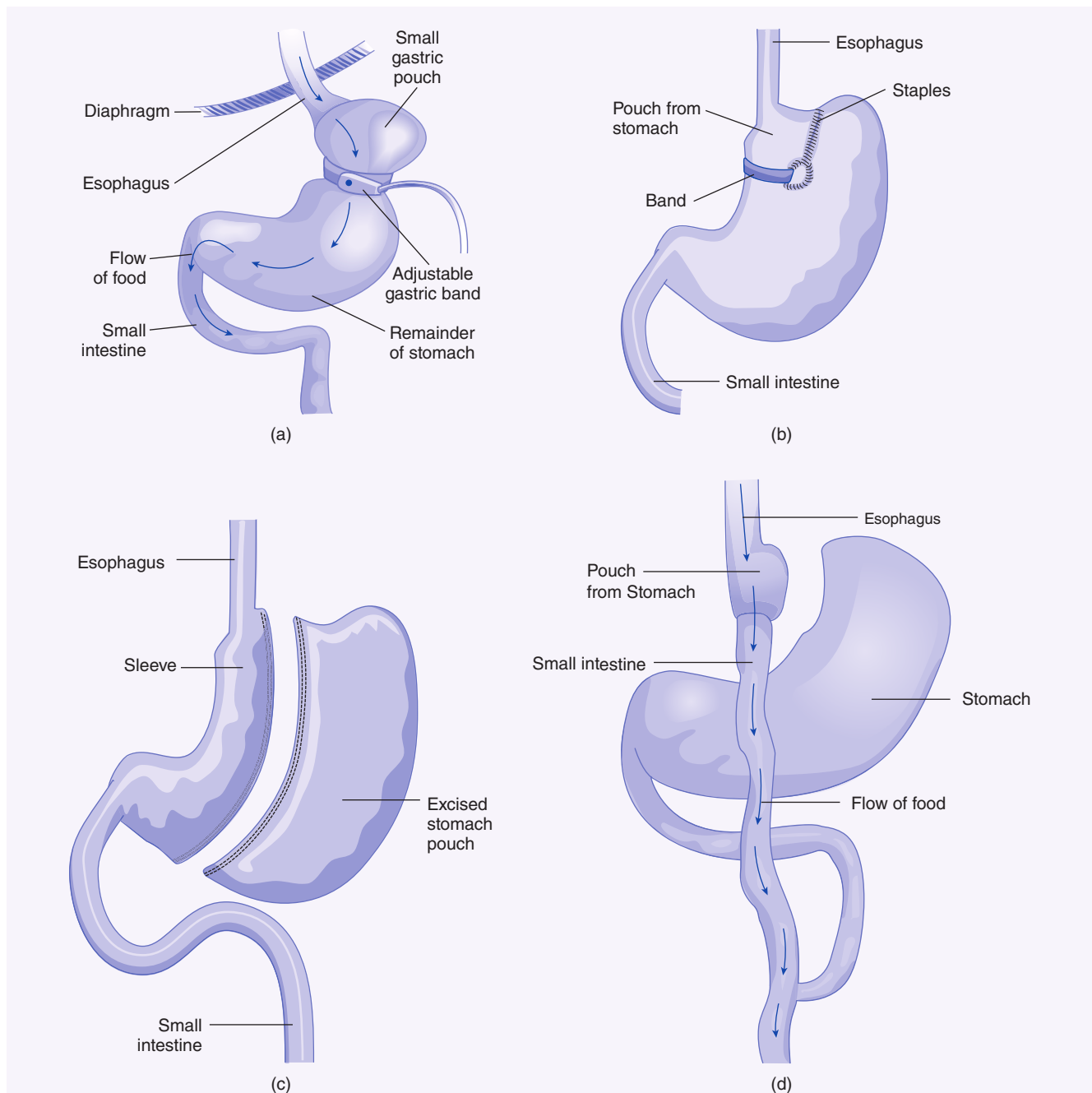


FIGURE 1 Various bariatric surgeries used for weight reduction. (a) Gastric or lap banding (b) Gastroplasty (c) Gastric sleeve (d) Roux-En-Y.

Bariatric surgery can lead to significant reductions in weight, (up to 40% weight loss from initial weight) and also decrease adiposity. Additionally, diseases associated with obesity, such as arthritis, Type II diabetes, and heart disease may be attenuated with the weight loss.

► Lymphatic System

Absorption of certain nutrients occurs via the lymphatic system. In particular, lipid breakdown products and other fat-soluble vitamins are packaged into small lipids and proteins containing components

of *chylomicrons* (See Chapter 5). Special lymphatic structures, or *lacteal capillaries*, are found within the villi of the small intestine. Later, they converge within the submucosa of the small intestine to form lacteals. The lacteals are important because chylomicrons are too large to enter the blood capillaries

that eventually end up in the portal blood supply. The network of lacteals converge into larger structures within the lymph system and the lymph fluid enters the circulatory system through the thoracic duct under the right arm. Other nutrients enter the blood supply directly via the portal vein and go to the liver first. With the lymphatic system, the material is emptied directly into the blood circulation, which then goes directly to the heart, bypassing the liver upon entry.

The lymphatic system has other functions, such as removal of fluid from interstitial tissues, transport of white blood cells, and antibodies. The lymph system plays a critical role in the immune system. The thymus is a lymph organ where T cells are matured. Later, we will discuss more of the lymph system on water as it relates to edema.

BEFORE YOU GO ON . . .

1. What are the three phases of digestion?
2. What is the relationship of R proteins and intrinsic factor in the stomach? Where are R proteins produced?
3. What is the role of the pancreas and gallbladder secretions in digestion?
4. Does the small intestine have any DIRECT enzymatic role in the breakdown of nutrients prior to absorption?
5. What is the role of the large intestine in digestion and absorption? What accounts for the color of fecal material?
6. With respect to digestion and absorption, what is the major function of the lymphatic system?



CLINICAL INSIGHT

Nutrition Disorders with Nutrition Implications of the GI System

Many nutrition interventions or diet therapies are linked to a wide spectrum of diseases of the gastrointestinal tract, including organs such as the liver, gall bladder, and pancreas that influence digestion and absorption. Some of those diseases require enteral feedings to help provide adequate nutritional support. The esophagus can develop conditions that lead to significant digestive problems. **Barrett's syndrome**, a precancerous condition and esophageal cancer, often results in removal of the esophagus and resection of the remaining esophageal tissue with the stomach. Nutrition support and lifetime modification of the type of feedings are essential. Gastroesophageal reflux disease, discussed already, is due to lower pressure of the lower esophageal sphincter muscle. Often, another condition with clinical implications is development of hiatal hernias, whereby a portion of the stomach moves to the thoracic cavity through the diaphragm. This can also lead to sensations of heartburn that may respond to dietary intervention. Esophagitis or inflammation of the esophagus can result from these diseases.

The stomach can develop various pathologies that impact the well-being of nutrition and require nutrition support. Gastric and peptic ulcers are common and diet intervention (along with some pharmacologic therapies) can alleviate many of the symptoms. Ulcers may also occur in the duodenum of the small intestine. In the stomach, many of the ulcers are caused by the organism *Helicobacter pylori*, which can induce inflammation of the gastric mucosa and lead to ulceration. Antibiotics are useful in treating this but, historically, nutrition support has been used to alleviate many of the symptoms. Cancer of the stomach is perhaps the one medical condition that requires significant medical nutrition therapy because, many times, portions of the affected stomach are surgically removed. Dumping syndrome is a common postoperative disorder that also needs to be kept in check via medical nutrition therapy.

Disorders/diseases of both the small and large intestines often require medical nutrition therapy. Flatulence is a common problem due to swallowing air while eating, bacterial fermentation of carbohydrates, or even decreased gastric motility, which may contribute to the problem. A common disorder among westerners is constipation, which can be minimized with appropriate lifestyle adjustments. A low-fiber diet may contribute to constipation and increasing dietary fiber is often used to alleviate constipation along with enhanced hydration. However, it is important to rule out other possible etiologies, such as neuromuscular disorders, interactions with other medications, and other diseases. Diarrhea, which often has a multitude of etiologies, often needs monitoring in order to prevent dehydration and significant loss of electrolytes. Inflammatory diseases or conditions, infections, medications, or increased osmotic pressure due to overconsumption of sugary foods can lead to diarrhea. On the other hand, malabsorption of nutrients, such as fat, leads to **steatorrhea**, or fatty stools.

Crohn's disease affects the distal part of the ileum and parts of the large intestine. **Ulcerative colitis** is most likely contained in the distal large intestine. Both of these diseases are **inflammatory bowel disease (IBD)**. Diarrhea and

fever are common to both disorders and malnutrition is common. Crohn's disease is more difficult to manage and is lifelong compared with ulcerative colitis.

There are also a number of brush border diseases that affect the ability of nutrients to be absorbed from food. A good example is lactose intolerance, which leads to diarrhea due to increased osmotic pressure created by undigested lactose; and increased flatulence due to fermentation by bacteria.

Celiac sprue is another common gastrointestinal disorder. **Gluten-sensitive enteropathy** and **tropical sprue** are the two types. The former has gained wide attention in the development of gluten-free diets by eliminating certain grains such as wheat products from the diet. Tropical sprue appears to be geographically restricted and likely due to infectious agents compared with gluten-sensitive enteropathy. In both cases, diarrhea is common and loss of electrolytes and dehydration must be carefully monitored.

In addition to the issues above, there are a number of liver, gallbladder, and pancreatic disorders that have far-reaching nutrition implications. **Hepatitis**, whether viral (acute) or chronic, are serious diseases. Viruses A and E are infectious and common when there are fecal contaminants to food or liquids consumed. The other forms are spread by exchange of body fluids. Chronic hepatitis may be of an autoimmune origin or due to medicines or toxins. Nonalcoholic fatty liver disease may be classified into either **nonalcoholic fatty liver disease** or **nonalcoholic steatohepatitis**. Both of those disorders are characterized by the appearance of lipid droplets in the hepatocytes. Nonalcoholic fatty liver disease may be due to genetic anomalies, obesity, or diabetes. This can lead to cirrhosis, fibrosis, and liver cancer. Nonalcoholic steatohepatitis is similar in presentation but has much more fibrosis tissue. It is common that nonalcoholic fatty liver disease leads to nonalcoholic steatohepatitis.

The most common liver disease in the United States is **alcoholic liver disease**. In the metabolism of alcohol, acetaldehyde is produced as a byproduct, which results in significant toxicity to hepatocytes (See Chapter 5). Fat accumulation, inflammation, and, finally, liver cirrhosis are the stages of this disease. Regardless of what liver disease a person acquires, the most significant nutritional consequence is malnutrition. Diagnosing the disease and putting into place a Medical Nutrition Therapy plan is essential. Algorithms are available to help the dietitian develop a nutrition plan based on the liver disease.

The major gallbladder disease of nutrition consequence is **cholestasis**. Little or no bile is secreted. This is due to an obstruction. There are several types of cholestasis: **cholelithiasis**, **cholecystitis**, and **cholangitis**. Production of gall stones leads to cholelithiasis. Inflammation of the gallbladder is cholecystitis, and inflammation of the bile ducts is cholangitis.

Regarding the pancreas (exocrine), **pancreatitis** is the most common disorder. Chronic or severe pain may be present and can be severe enough to lead to vomiting. Medical Nutrition Therapy will depend on whether the condition is acute or chronic.

► Here's What You Have Learned

1. The digestive tract is a 6.5- to 8.5-meter (22- to 28-foot) tube that extends from the mouth to the anus, and the lumen is considered to be outside of the body. The wall of the digestive tract has several distinct layers composed of enterocytes, smooth muscle cells, neurons, and lymphatic cells
2. Several paracrine, endocrine, and exocrine tissues and organs support digestive activities, including the salivary glands, pancreas, liver, and gallbladder. The gastrointestinal system as a whole produces several liters of digestive juices daily
3. The three general phases of digestion are the cephalic, gastric, and intestinal phases. The cephalic phase occurs in the presence of the thought, smell, and taste of food. The gastric and intestinal phases are the result of distention of the stomach wall and mechanical and chemical events in the intestines
4. Digestion is a complex synergy of the physical actions of chewing, mixing, and moving and the chemical actions of saliva, enzymes, and emulsifiers. Digestion enables complex food systems and molecules to be simplified and reduced in size, allowing for efficient absorption
5. Absorption refers to the movement of nutrients from the digestive tract into the blood or lymphatic circulations, whereas the concept of bioavailability also includes the uptake and utilization of a nutrient by cells or tissue
6. Perceptions of hunger and satiety involve multiple hormonal and neurologic signals, including cholecystokinin, neuropeptide Y, ghrelin, insulin, and leptin. Despite a growing understanding of those signals, regulation of feeding is not enough to limit excessive weight gain
7. The pancreas produces and secretes more protein (protein per gram of tissue) than any other

- organ. Digestive enzymes are produced and stored as inactive zymogen molecules to prevent digestion of the cells that produce them. En route to the small intestine, digestive enzymes mix with bile derived from the gallbladder and liver in the common bile duct
8. Bile is a watery composite of substances such as bile acids, bilirubin, cholesterol, fatty acids, phospholipids, electrolytes, and bicarbonate. During interdigestive periods, bile flow from the liver is routed primarily through the cystic duct into the gallbladder for concentration and storage. The remaining bile flows to the small intestine
 9. The large intestine absorbs water and electrolytes from the entering content, which happens predominantly in the proximal half, and stores fecal matter until defecation, which occurs in the distal half
 10. Different types of bacteria are found along the length of the digestive tract, depending on the environmental conditions of the segment and the properties of the bacterial species, with the highest concentration found in the colon. Many bacteria are considered supportive of human health in some manner and are referred to as probiotic. Some plant substances promote beneficial bacteria and decrease the growth of deleterious pathogens. These compounds are referred to as prebiotics
 11. The lymphatic system is important in the absorption of lipids
 12. Diseases of many types affect components of the gastrointestinal system. For many of these diseases, nutrition support is critical to the outcome and course of these diseases

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