Mouth and Esophagus 8.1

Learning Objectives

- State the overall function of the gastrointestinal system
- Describe the role of sphincters in the gastrointestinal tract
- Name the major parts of the gastrointestinal tract from mouth to anus, in order
- Describe the overall function of liver, gallbladder, and pancreas in gastrointestinal function
- List the major purposes of chewing food
- Distinguish between serous and mucus saliva
- List the major purposes of saliva
- Describe the three major components of salivary glands (acinus, intercalated duct, and striated duct)
- Explain why salivary composition varies with flow rate
- Describe CNS control of salivation and its major sources of variation
- Describe the pharyngeal phase of swallowing
- Describe peristalsis
- Distinguish between primary peristalsis and secondary peristalsis
- Describe the overall layers of the gastrointestinal tract
- Describe the location and function of the intestinal nerve plexuses
- Define achalasia and GERD

THE GASTROINTESTINAL SYSTEM SECURES NUTRIENTS FOR MAINTENANCE, MOVEMENT, AND GROWTH

In thermodynamics, entropy S is a state variable (meaning that it depends solely on the state and not on the path to that state) that is related to the degree of disorder. Boltzmann's tomb in the central cemetery in Vienna has inscribed on it his famous equation:

$$S = k \ln \Omega \quad [8.1.1]$$

where Ω is the number of indistinguishable ways of obtaining a state. This is related to the probability of obtaining a state. Living beings are highly ordered and the probability of assembling one spontaneously from scratch is pretty low. According to Boltzmann's formulation, living things are characterized by low entropy. All natural processes require that the entropy of the universe increases—they proceed from less probable to more probable arrangements. Local decreases in entropy (such as occurs in the assembly of living things) are possible only by increasing the entropy of the surroundings to compensate for the local decrease. **Living things maintain their highly ordered structure by taking in energy and degrading it (producing entropy)**. Our assembly and continued existence as a low entropy state far from equilibrium depends on a throughput of energy that we degrade continuously to increase the entropy of the universe. We secure this energy and the chemical building blocks of our structure through digestion and absorption of the food we eat. This is accomplished by the gastrointestinal (GI) system. **The function of the GI tract is to extract the nutrients we need from ingested food.** These nutrients maintain our highly ordered structure far away from equilibrium, provide energy for our activity, and provide the raw building materials needed for growth from birth to adulthood. The GI tract also provides another route for the excretion of metabolic wastes.

NUTRIENTS ARE NECESSARY MATERIALS THAT MUST BE SUPPLIED BY FOOD

"Nutrient" is defined as any substance that is used by the body that must be supplied in adequate amounts from consumed foods. There are six classes of nutrients:

1. **water**
2. **fats**
3. **proteins**
4. **carbohydrates**
5. **vitamins**
6. **minerals.**

Probably the single most important function of the gastrointestinal tract is to absorb sufficient water to replace losses from the lungs, skin, urine, and feces. We produce water from metabolism, but this is very much less than what is needed to replenish losses. Fats, proteins, and carbohydrates are macronutrients, because we require them in large quantities, both as a source of energy and as building blocks for the tissues. The macronutrients are first broken down into simple constituents by digestion, and these simple constituents are then absorbed into the blood stream for use by peripheral tissues. Some of these building blocks can be synthesized, but the ones that we can't make are called "essential," meaning that they must be obtained directly

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TABLE 8.1.1 Daily Requirements for Nutrients for Humans

Water	Fats	Proteins	Carbohydrates	Vitamins	Minerals
3.7 L	**20–35% of total energy** *Essential fatty acids*: Linoleic acid (18:2 $\omega - 6$) **17 g** α-Linolenic acid (18:3 $\omega - 3$) **1.6 g**	**56 g** *Essential amino acids*: Histidine Isoleucine Leucine Lysine Methionine Phenylalanine Threonine Tryptophan Valine	**130 g**	*Fat-soluble vitamins*: Vitamin A **900 μg** Vitamin D **15 μg** Vitamin E **15 mg** Vitamin K **120 μg** *Water-soluble vitamins*: Vitamin C **90 mg** Thiamine (B1) **1.2 mg** Riboflavin (B2)**1.3 mg** Niacin (B3) **16 mg** Pantothenic acid (B5) **5 mg** Vitamin B6 **1.3 mg** Biotin (B7) **30 μg** Folic acid (B9) **400 μg** Vitamin B12 **2.4 μg** Choline **550 mg**	Sodium **2.3 g** Potassium **4.7 g** Chloride **2.3 g** Calcium **1000 mg** Phosphorus **700 mg** Fluoride **4 mg** Iodine **120 μg** Iron **8 mg** Copper **900 μg** Selenium **55 μg** Magnesium **400 mg** Manganese **2.3 mg** Molybdenum **45 μg** Zinc **11 mg** Chromium **35 μg**

The values are given per day for a healthy male between 19 and 30 years old. Value for overall fat is given as a percent of total dietary calories. For all other nutrients, values given are the **Recommended Dietary Allowances** or **RDA** (in bold black), which is the average daily intake that is sufficient to meet the nutrient requirements of at least 97.5% of all healthy individuals within the group. RDAs are calculated from the **EAR**, the **estimated average requirement**, plus twice the standard deviation for the EAR. If there is insufficient data to establish an EAR, an **AI** or **adequate intake** is developed and given for some nutrients (bold blue).

from the diet. The subsets of the six classes of nutrients are given in Table 8.1.1. The **RDA** (recommended dietary allowance) or **AI** (adequate intake) is given for each. The RDA varies with age, body size, gender, and reproductive status (pregnant or lactating). The figures given are for a 20-year-old 70-kg male.

THE GASTROINTESTINAL SYSTEM IS A TUBE RUNNING FROM MOUTH TO ANUS

Our basic body plan is that of a hollow cylinder with thick walls. The outside is the **integument** or skin; the thick wall encases the bones, muscles, nerves, and all other organs, and the inner layer is the GI system. As shown in Figure 8.1.1, the GI system is a long tube, with various shapes and bulges, that runs from the mouth to the anus. Topologically, the **lumen**, the space enclosed by the tube, and all food in the lumen, is outside of the body. The GI system moves ingested food along the tube, breaks it down into usable materials, and absorbs these building blocks into the blood. Unabsorbable materials and other wastes are excreted in the feces.

THE GASTROINTESTINAL SYSTEM PROPELS MATERIAL BETWEEN DEFINED AREAS DEMARCATED BY *SPHINCTERS*

Smooth muscles embedded in the walls of the GI tract squeeze the food and move it along. Neurons in the gut wall control and coordinate the smooth muscle contractions. Movement of material between regions is controlled in part by a series of **sphincters**, which are bands of smooth muscle that generally are tonically contracted, narrowing the lumen. Food in the mouth is chewed and lubricated and then swallowed. The swallowed **bolus** of food enters the esophagus through the **upper esophageal sphincter**. The **esophagus** transports materials to the **stomach**. The **lower esophageal sphincter (LES)**, at the junction of esophagus and stomach, controls entry to the stomach and reflux of stomach contents into the esophagus. Digestion, the breakdown of food into its constituent parts, begins in the mouth and continues in the stomach. The stomach holds food and releases it gradually into the **small intestine**. The **pyloric sphincter**, at the junction of the stomach and the first segment of the small intestine, controls stomach emptying. The small intestine provides the major part of digestion and absorption of nutrients. It consists of three segments: the **duodenum**, **jejunum**, and **ileum**. The ileum dumps its contents into the **large intestine**, which consists of the **cecum, ascending colon, transverse colon, descending colon**, and **sigmoid colon**. The **ileocecal sphincter** controls the movement of material from the ileum into the large intestine and prevents the backward movement of material from the colon into the ileum. Eventually the material that is not absorbed moves into the **rectum** from where it is expelled from the body during **defecation**. Defecation is controlled by two sphincters, the **internal anal sphincter** and the **external anal sphincter.** Thus the entire GI tract consists of a series of specialized areas of a tube that is invested with sphincters that control the movement of materials between the different regions. The upper esophageal sphincter and the external anal sphincter are both composed of skeletal muscle (even though they do not connect to bone). The external anal sphincter is controlled voluntarily. The movement of materials through the GI tract is largely unconscious

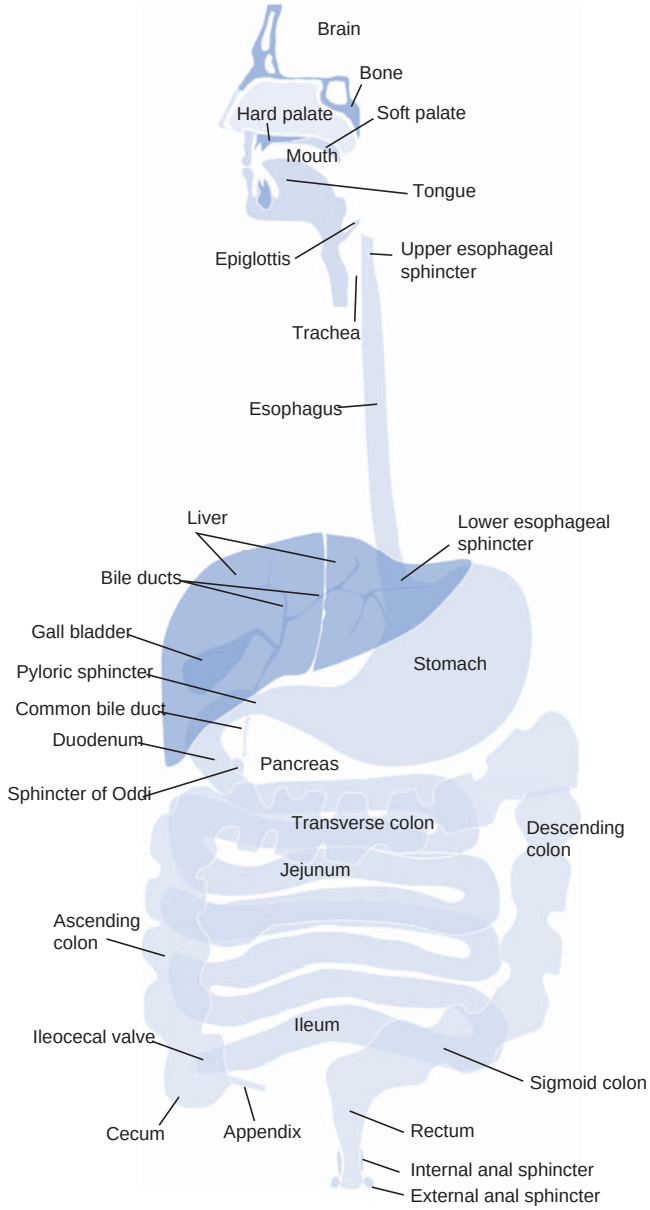

FIGURE 8.1.1 Overall view of the GI system. Food enters the mouth where it is chewed and lubricated and then swallowed. The food passes through the upper esophageal sphincter into the esophagus, which propels it through the LES into the stomach. The stomach in turn moves material through the pyloric sphincter into the first part of the small intestine, the duodenum. The duodenum leads into the jejunum and ileum, with no sphincters separating these regions of the small intestine. The ileum drains into the cecum of the large intestine at the ileocecal sphincter or valve. Material sequentially traverses the ascending colon, transverse colon, descending colon, and sigmoid colon before it enters the rectum prior to defecation. Defecation is controlled in part by two sphincters, the internal anal sphincter and the external anal sphincter. The liver contributes to GI function by secreting bile. Bile flows down the hepatic bile ducts to the gallbladder where it is stored between meals. During meals the gallbladder empties into the duodenum through the common bile duct. The pancreas secretes a variety of digestive enzymes that enter the duodenum through the pancreatic duct, which joins the common bile duct just before it enters the duodenum. The sphincter of Oddi controls bile and pancreatic juice entry into the duodenum.

and involuntary, whereas we begin and end the process (by eating and defecation) through voluntary control.

THE LIVER AND PANCREAS SECRETE MATERIALS INTO THE INTESTINE TO AID DIGESTION AND ABSORPTION

The **liver** and the **pancreas** secrete materials into the intestine to aid digestion or absorption of nutrients. The pancreas lies in the angle between the stomach and the duodenum, and it secretes a watery fluid that contains a host of pancreatic enzymes that break down food into its parts. The secretion flows along the pancreatic duct, which enters the duodenum. Another sphincter, the **sphincter of Oddi**, controls entry of pancreatic juice into the duodenum.

Liver cells make **bile** that flows down **hepatic bile ducts** to be stored in the **gallbladder**. After a meal, the gallbladder contracts and squeezes out the stored bile that travels down the **common bile duct** where it joins the pancreatic duct just before it enters the duodenum. The bile helps digest and absorb fats and also serves as an excretory route for a variety of materials.

THE TRIGEMINAL NUCLEUS IN THE BRAINSTEM SETS THE RHYTHM OF MASTICATION

The muscles of the jaw, lips, tongue, and cheek all participate in chewing. Most of these muscles are innervated by the **trigeminal nerve** (**cranial nerve V**). The **masseter** muscle originates on the inner surface and anterior two-thirds of the zygomatic bone (the bone that forms the cheekbone) and inserts onto the ramus of the mandible (the back and lower part of the lower jaw). The **temporalis** muscle is a large fan-shaped muscle that originates on the temporal bone of the skull and inserts on the coronoid process of the mandible. The **medial pterygoideus** is synergistic with the masseter in closing the jaw. It originates on the pterygoid plate and inserts on the inner side of the ramus of the mandible. Contraction of the temporalis muscle abducts the mandible to the side, whereas contraction of the medial pterygoideus pulls the mandible medially. These muscles are paired, and so contraction of the left medial pterygoideus pulls the mandible to right, but only if the right medial pterygoideus is relaxed. Proper synchronization of these muscles produces the grinding motion of the teeth. The **digastric muscle** is a paired muscle that inserts on the mastoid process, part of the temporal bone behind the ear, and the suture that joins the two halves of the lower jaw. It is mainly responsible, with accessory muscles, for opening the jaw. It has two bellies that are connected to an intermediate tendon that forms a connective tissue sheet that also connects to the hyoid bone. When the hyoid bone is pulled from below, contraction of the digastric muscle opens the jaw. The trigeminal nerve innervates the anterior part of the digastric, whereas the **facial nerve, cranial nerve VII**, innervates the posterior belly.

Coordination of muscles for chewing is accomplished by a neural center in the brainstem, with parts in the midbrain, pons, and medulla. The final pathway to the

masseter and digastric muscles is provided by two motor sections of the nucleus of the trigeminal nerve, NV_{mot}. Output of these motor neurons is controlled by a variety of inputs from other areas of the nucleus of the trigeminal nerve (NV) that relay sensory signals from the muscles, teeth, and commands from the **cortical masticatory area (CMA)** in the primary motor cortex. Part of the NV, NV_{spnr} contains a **central pattern generator (CPG)** that sets the rhythm for chewing but is modulated by inputs from sensory afferents such as the stretch receptors in the respective muscles. The overall control of mastication is shown in Figure 8.1.2. Other accessory muscles are also involved. The tongue positions food under the teeth while keeping out of the way of the teeth, and cheek muscle (buccinator) helps keep the food there.

The origin of the masticatory rhythm remains an active field of investigation. Current thought is that some cells in the NV_{snpr} have intrinsic bursting abilities that make it act like a pacemaker. The ionic mechanisms that produce this bursting behavior are not yet clear. How the neurons act in concert to transmit this rhythm to sets of antagonistic muscles is also not yet known. Neuronal networks allow emergence of new network properties because the intrinsic rhythm can be modulated by synaptic contacts. A working hypothesis of the CPG for mastication is shown in Figure 8.1.3.

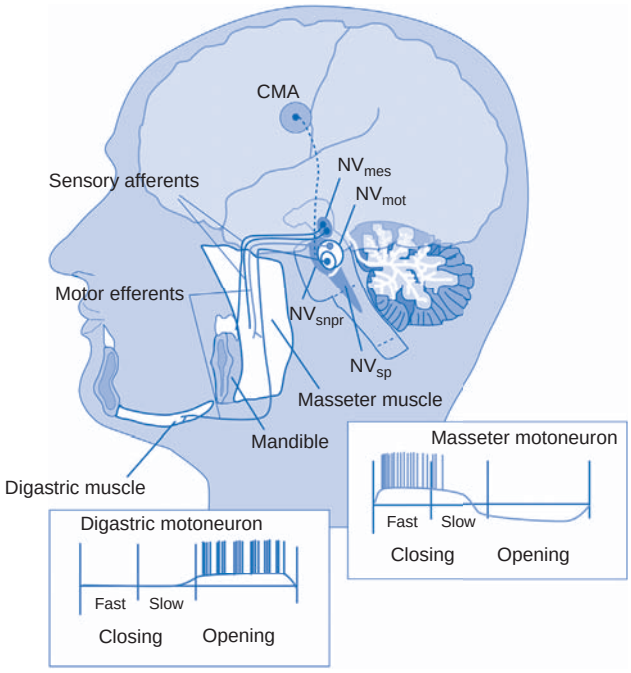

FIGURE 8.1.2 Nervous control of mastication. The masseter muscle helps close the jaw. The digastric muscle helps open it. The trigeminal nerve (cranial nerve V) innervates both muscles. Motoneurons in the motor part of the nucleus of the trigeminal nerve (NV_{mot}) drive the muscles. NV_{mot} receives inputs from NV_{mes} that contains primary sensory afferents from stretch receptors within the muscles and from the teeth and NV_{spnr} that contains the central pattern generator. The CPG receives input from the cortical masticatory area (CMA) in M1 and feedback through sensors. Motoneurons for the masseter muscle produce the trace shown in the figure: a depolarization followed by a train of action potentials occurs during the closing phase and these gradually decrease in frequency at the beginning of the slow phase of jaw closing. During the opening phase the cells are hyperpolarized. The horizontal line indicates the resting membrane potential. Motoneurons for the digastric muscle show little change in the membrane potential during jaw closing, followed by a depolarization and train of action potentials during the opening phase. These eventually fatigue and the motoneuron repolarizes. *From P. Morquette et al., Generation of the masticatory central pattern and its modulation by sensory feedback.* Progr. Neurobiol. ***96***:*340–355, 2012.*

CHEWING HAS MULTIPLE PURPOSES

- **Chewing grinds food**: The jaw muscles can produce a force of up to 700 N on the molars and about 350 N on the incisors. This is enough to crack a hazelnut. These forces are concentrated in the small surface area of occlusive contact of the teeth.
- **Grinding increases the surface area**: Because digestion occurs at the surfaces of the ingested food, increasing the surface area increases the speed of digestion. However, this makes little difference to the completeness of digestion. Chunks of meat that are swallowed whole are as completely digested as chunks that are thoroughly chewed, but chewing reduces the time for digestion.
- **Chewing reduces food size so that it can be swallowed**: Wild predators generally rip meat off their kills with their canine teeth and swallow large pieces. We tend to choke on such pieces. Chewing breaks

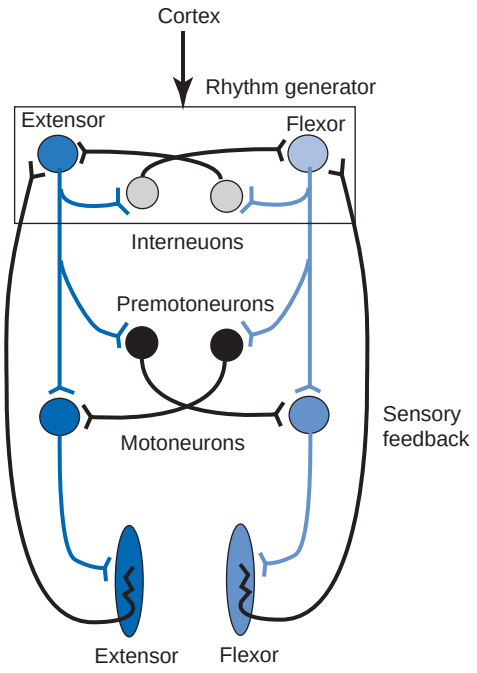

FIGURE 8.1.3 Model of the nervous control of mastication. Cells in the NV_{snpr} have intrinsic rhythm or pacemaker behavior and make up the rhythm generator. All colored connections are excitatory. All black connections are inhibitory. Mutual inhibition through interneurons assures alternating activity between extensors and flexors. Fatigue of the interneurons switches between the two centers. The first level of connections generates the rhythm, the second level composed of premotoneurons and motoneurons determines the envelope of the bursting pattern of the motoneurons. *From P. Morquette et al., Generation of the masticatory central pattern and its modulation by sensory feedback.* Progr. Neurobiol. ***96***:*340–355, 2012.*

Clinical Applications: Temporomandibular Joint Syndrome

Temporomandibular joint syndrome (TMJ), also called temporomandibular disorder (TMD), is the most common source of pain after toothache. It can be classified broadly as: (1) secondary to myofacial pain and dysfunction (MPD) and (2) secondary to a primary articular disease. It is estimated that TMD affects some 10 million people in the United States alone. It affects women, 4:1, over men. The highest incidence is among young adults, especially women between 20 and 40 years old.

The symptoms of TMD include the following: (1) pain, usually around the ears, that is associated with chewing; the pain may radiate to the head, but it is not like a typical headache; (2) clicking, popping, or snapping sounds associated with pain and movement of the temporomandibular joint; (3) episodes of limited jaw opening or locking; the locking may be in the open or closed position and can be very painful; and (4) associated symptoms of neck pain or stiffness, shoulder pain, dizziness, and ear pain.

MPD comprises the majority of cases of TMD. X-rays of the jaw show no destructive changes of the temporomandibular joint. It has a variety of causes. Frequently, MPD is associated with **bruxism** (grinding of the teeth) and jaw clenching due to stress or anxiety. The pain, tenderness, and spasm of the mastication muscles are due to muscular hyperactivity and dysfunction due to malocclusion. Psychological factors increase the risk of MPD. Persons with MPD tend to exhibit obsessive–compulsive behavior and are more likely to deny problems in their life.

TMD caused by true articular disease is most often due to disk displacement. The temporomandibular joint is a gliding joint formed by the condyle of the mandible and the squamous (flat) part of temporal bone. The articular surface of the temporal bone forms a convex articular eminence anteriorly and a concave articular fossa posteriorly. The articular surface of the mandible is the top of the condyle. An articular disk separates the mandible from the temporal bone and divides the joint cavity into two small spaces. Degenerative joint disease, rheumatoid arthritis, dislocations, infections, and neoplasias (cancers) are all possible causes of individual cases of TMD due to articular disease.

the food into pieces small enough to pass into the pharynx.

- **Chewing breaks cell walls of vegetative matter**: The cellulose cell walls of vegetative matter resist digestion because we lack the enzymes to break down cellulose. The crushing force of the teeth breaks down these cell walls and releases the cell contents for digestion.
- **Chewing takes the edges off food particles**: Breaking the food into smaller pieces and crushing it between the teeth helps prevent food particles from excoriating the gut lining.
- **Chewing mixes the food with the saliva**: The saliva moistens the food, lubricates it in preparation for swallowing, and allows us to taste the food.
- **Chewing moves food around so that the taste buds can sample it**: The taste buds sense only dissolved substances. Chewing mixes the saliva with the food and moves the food around in the mouth. Both of these actions present material to the taste buds so that they can be sampled. In addition, mechanoreceptors on the palate, tongue, and cheek walls create a "mouth feel" for the food that forms part of the hedonistic enjoyment of food and informs the brain when the food has the proper consistency for swallowing.

SALIVA MOISTENS, LUBRICATES, DIGESTS, AND PROTECTS

There are two general types of salivary glands: **serous glands** secrete mainly a watery fluid; **mucus glands** secrete more viscous saliva that contains **mucin**. Mucin is a class of high molecular weight glycoproteins that are expressed by epithelial tissues. They consist of a variable number of tandem repeat sequences that are rich in serine and threonine that provide hydroxyl groups to which oligosaccharide chains are O-linked.

The **parotid gland** is the largest of the salivary glands and is located at the back of the jaw between the angle of the jaw and the ear. The parotid gland secretes up to 50% of the saliva volume and secretes only serous saliva. These serous salivary glands also secrete α-amylase, an enzyme that hydrolyzes α-1,4-glycosidic linkages in starch.

The **submandibular glands** lie under the mandible and consist of a mixture of serous- and mucin-secreting cells. The **sublingual glands** lie under the tongue and are also a mixture of serous- and mucin-secreting cells. In humans the submandibular gland appears to cosecrete mucin and TFF3, one of three kinds of TFF-peptides. Its physiological role is not yet established; it seems to alter the **rheological** properties of saliva (its ability to flow), and it may also help repair injured parts of the GI tract.

The three major salivary glands (parotid, submandibular, and sublingual) account for about 90% of salivary secretion. A number of minor glands contribute the remaining 10%. Although serous lingual glands secrete small amounts of salivary **lipase**, it has little functional importance in humans. The location of the major salivary glands is shown in Figure 8.1.4.

The major functions of saliva are as follows:

- **Saliva lubricates food**: The watery secretion of saliva moistens food, making it easier to swallow. In addition, mucins make the food slippery, making it easier to swallow.
- **Saliva begins digestion**: Salivary amylase and lipase begin digestion even before the food leaves the mouth.
- **Saliva aids in speech by keeping the mouth moist**: By keeping the moving parts moist, saliva aids in the movement of lips and tongue both in the action of chewing and in speech.

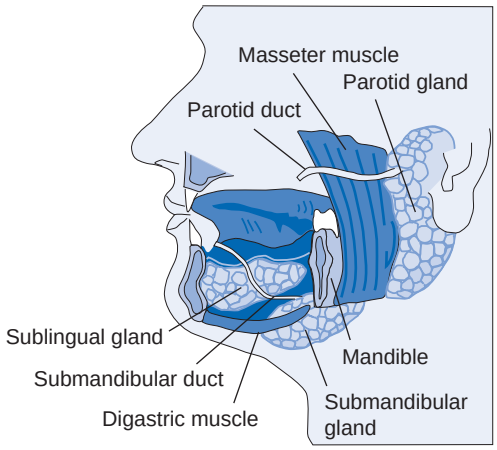

FIGURE 8.1.4 Location of the main salivary glands. The parotid gland is the largest, is located at the back of the jaw between the angle of the jaw and ear, and secretes only serous saliva. It drains into the roof of the mouth through the parotid duct (Stenson's duct). The submandibular gland lies under the mandible and is a mixture of serous and mucin-secreting cells. It drains into the mouth under the tongue through the submandibular duct (Wharton's duct). The sublingual glands lie under the tongue and also are a mixture of serous and mucin-secreting cells.

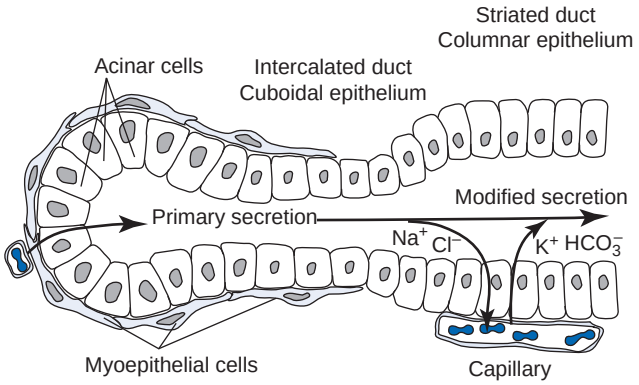

FIGURE 8.1.5 Schematic diagram of a salivary gland unit and the mechanisms of saliva secretion and modification. Saliva produced by acinar cells is isotonic with plasma. The lumen of the acinus leads to intercalated ducts that direct the saliva through striated salivary ducts where the fluid is modified by reabsorption of Na^+ and Cl^- and secretion of K^+ and HCO_3^-. The resulting saliva is hypotonic to plasma.

- **Saliva buffers mouth pH**: Saliva pH ranges from 6 to 8, with more alkaline pH at high salivary secretion rates. It contains HCO_3^-, phosphate, and proteins that protect the hard and soft tissues of the mouth against large pH changes by binding excess H^+ ions.
- **Saliva keeps the mouth clean**: The continuous production of saliva washes the mouth. This helps flush away food particles and reduces dental caries.
- **Saliva helps prevent infections**: Saliva contains a variety of antibacterial and antifungal components. These include **lysozyme**, **lactoferrin**, **myeloperoxidase, salivary peroxidase**, **immunoglobulin A (IgA)**, histatins, **statherin, and alpha and beta defensins**. Dry mouth, or **xerostomia**, is associated with infections of the buccal mucosa and with dental caries. The lysozyme destroys bacterial cell walls. Lactoferrin reduces bacterial growth by complexing essential iron. The peroxidases produce hydrogen peroxide (H_2O_2) and hypochlorus acid (HOCl) that are antibacterial. Histatin 5, in particular, inhibits the growth of *Candida albicans*, an oral fungus normally present whose overgrowth causes **thrush**. Statherins inhibit precipitation of calcium phosphate in saliva, and it also inhibit growth of anaerobic bacteria. Alpha defensin originates from neutrophils and beta defensins from epithelial cells. Both have antibacterial and antiviral effects. Secretory IgA has activity against bacteria but its significance is unknown as persons with hereditary lack of IgA show no increase in oral disease.
- **Saliva may help heal mouth and esophageal damage:** The mouth repeatedly experiences wounds that range from cheek, tongue, and lip biting to tooth extraction, but these wounds heal much more quickly than skin wounds with less scarring and infrequent infections. First, saliva contains tissue factor that aids in hemostasis that limits bleeding and exposure of the circulation to infectious agents in the mouth. Second, in addition to the electrolytes and mucins, saliva also contains a variety of **growth factors**. Growth factors are polypeptides that help tissues repair themselves following injury. Saliva contains **epidermal growth factor (EGF)**, **fibroblast growth factor (FGF)**, **nerve-derived growth factor (NGF)**, vascular endothelial growth factor (VEGF), **transforming growth factor** α **(TGF-**α**)**, and **trefoil factor 3** (TFF3). All of these are thought to enhance healing in the mouth. Their function in protecting the esophagus from damage either by excoriation (scratching) by food particles, by acid reflux from the stomach, or by bacterial or viral agents is not yet established. The instinctive licking of wounds by humans and many other animals may be beneficial because of the healing factors found in saliva.

SALIVARY GLANDS PRODUCE AN ISOTONIC FLUID THAT IS SUBSEQUENTLY MODIFIED

The salivary glands are tubes that end in blind sacs (see Figure 8.1.5). Some of these sacs are shaped like grapes, from which they derive their name **acinus** (meaning "grape shaped"). Others end in a smaller cap of a tubular end piece. Cells in the acinus secrete a fluid that is isotonic with plasma and whose composition initially is independent of the flow rate. The acinar cells are connected by apical **tight junctions** that are permeable to cations. The acini lead into **intercalated ducts** that connect the acini to **striated ducts**. The intercalated ducts consist of cuboidal epithelial cells that may serve as a reservoir of stem cells for both acini and striated ducts. The striated ducts consist of columnar epithelial cells that possess deep infoldings of their basal membrane. These deep infoldings produce their striated appearance from which the striated ducts derive their name. These ducts modify the composition of the plasma by reabsorbing some components (Na^+ and Cl^-) back into the blood and secreting other components (K^+) into the saliva. The striated duct cells are impermeable to water. Reabsorption of Na^+ and Cl^- is not accompanied by the osmotic transport of water, resulting in hypotonic saliva.

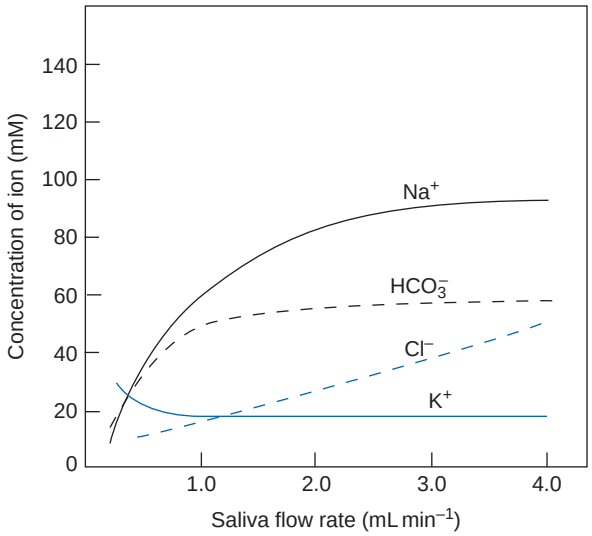

FIGURE 8.1.6 Composition of human parotid saliva as a function of flow rate. As flow increases, Na^+ and Cl^- concentrations increase toward plasma levels, whereas HCO_3^- concentrations level off and K^+ concentrations are less than at low flow rates. *Redrawn from J.H. Thaysen, N.A. Thorn, and I.L. Schwartz, Excretion of sodium potassium, chloride and carbon dioxide in human parotid saliva.* Am. J. Physiol. ***178***:155, 1954.

Myoepithelial cells cover the acini and line the outside of the intercalated ducts. Both sympathetic and parasympathetic fibers innervate them. They support the salivary gland structures and promote secretion by their contraction.

SALIVA COMPOSITION DEPENDS ON THE FLOW RATE

Because saliva is formed in two stages, production of an isotonic secretion and then modification during passage through the ducts, the composition of saliva varies with its rate of flow. Saliva flow varies from 0.1 mL min^{-1} during sleep to 4–6 mL min^{-1} during eating. Unstimulated saliva production during the day is about 0.3–0.4 mL min^{-1} and shows a circadian rhythm, peaking generally in mid-afternoon. Total salivary secretion has been estimated to be about 0.6 L day^{-1}. The composition of human parotid saliva as a function of saliva flow rate is shown in Figure 8.1.6.

THE SALIVARY NUCLEI OF THE MEDULLA CONTROL SALIVATION

Direct control of salivation occurs through the superior and inferior salivary nuclei located in the pons and medulla (see Figure 8.1.7). Parasympathetic

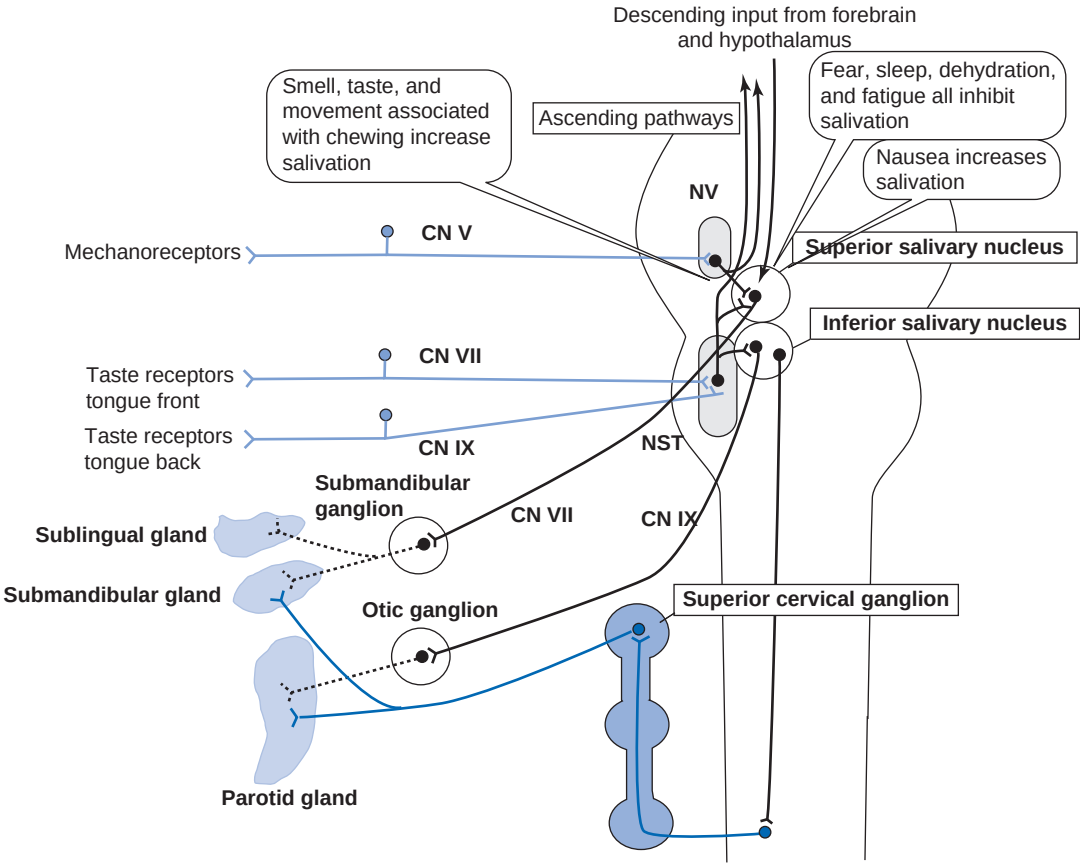

FIGURE 8.1.7 Nervous control of salivation. The superior and inferior salivary nuclei located in the pons and medulla directly control salivation. Preganglionic parasympathetic fibers from the superior salivary nucleus travel over the facial nerve, CN VII, to the submandibular ganglion and then to secretory cells in the submandibular and sublingual glands. Preganglionic fibers from the inferior salivary nucleus travel to the otic ganglion and stimulate parotid gland secretion. Sympathetic fibers exit the cord at T1, T2, and T3, travel up the sympathetic chain to the superior cervical ganglion, and then to the parotid and submandibular glands. Taste and mechanoreceptor afferents enter the nucleus of the solitary tract (NST) and NV, the nucleus of the trigeminal nerve, and modulate salivary secretion. Inputs from higher centers also modulate salivary secretion.

preganglionic fibers from the superior salivary nucleus travel over a branch of the facial nerve (CN VII) to the submandibular ganglion where they synapse onto postganglionic fibers that stimulate serous secretion of the sublingual and submandibular salivary glands. Preganglionic fibers from the inferior salivary nucleus travel over the glossopharyngeal nerve (CN IX) to synapse on postganglionic fibers in the otic ganglion, and these stimulate serous secretion of the parotid glands. The salivary nuclei are influenced by sensory afferents from the taste buds, olfactory receptors, and mechanoreceptors. Olfactory information enters via the olfactory nerve (CN I). The facial nerve (CN VII) transmits taste information from the anterior tongue; the glossopharyngeal nerve (CN IX) carries taste sensation from the posterior tongue. Both synapse on cells in the nucleus of the solitary tract (NST) which then connects to the salivary nuclei. The trigeminal nerve (CN V) carries mechanoreceptor signals to the trigeminal nucleus (NV), which then also connects to the salivary nucleus. Cells in the inferior salivary nucleus also stimulate sympathetic motor neurons in T1, T2, and T3 of the thoracic spinal cord. Their axons travel to the sympathetic chain and ascend to the superior cervical ganglion to synapse onto postganglionic fibers that stimulate the parotid and submandibular glands.

Higher centers of the brain, such as the forebrain and hypothalamus, can also influence salivation through inputs to the salivary nuclei. Fatigue, dehydration, sleep, fear, and mental depression all depress saliva flow. Nausea and appetizing odors stimulate saliva production. These higher centers receive sensory information from a variety of sources including the NST and NV in order to correctly instruct the salivary nuclei.

PARASYMPATHETIC STIMULATION RESULTS IN HIGH-VOLUME, WATERY SALIVA

Salivary glands are innervated by both the sympathetic and parasympathetic divisions of the autonomic nervous system and both stimulate secretion. Parasympathetic stimulation mainly increases the watery secretion, whereas sympathetic stimulation mainly increases protein secretion (see Figure 8.1.8).

Parasympathetic nerves contain a variety of neurotransmitters including acetylcholine, vasoactive intestinal polypeptide (VIP), and substance P. These nerves are associated with salivary glands and the vasculature that supplies the glands. Substance P and acetylcholine stimulate a watery secretion by activating a G_q mechanism that activates phospholipase C to split phosphatidylinositol-4,5-bisphosphate to diacylglycerol and inositol-1,4,5 triphosphate or IP_3. The released IP_3 binds to IP_3 receptors (IP_3R) on the endoplasmic reticulum and causes the IP_3R to release Ca^{2+} to the cytoplasm. The increased $[Ca^{2+}]$ is the final trigger that stimulates a variety of ionic transport mechanisms that result in increased secretion of primary saliva. In addition, parasympathetic stimulation releases **vasoactive intestinal peptide (VIP)** which is a potent vasodilator and **increases blood flow to the salivary glands**. Since the saliva originates from the blood, the increased

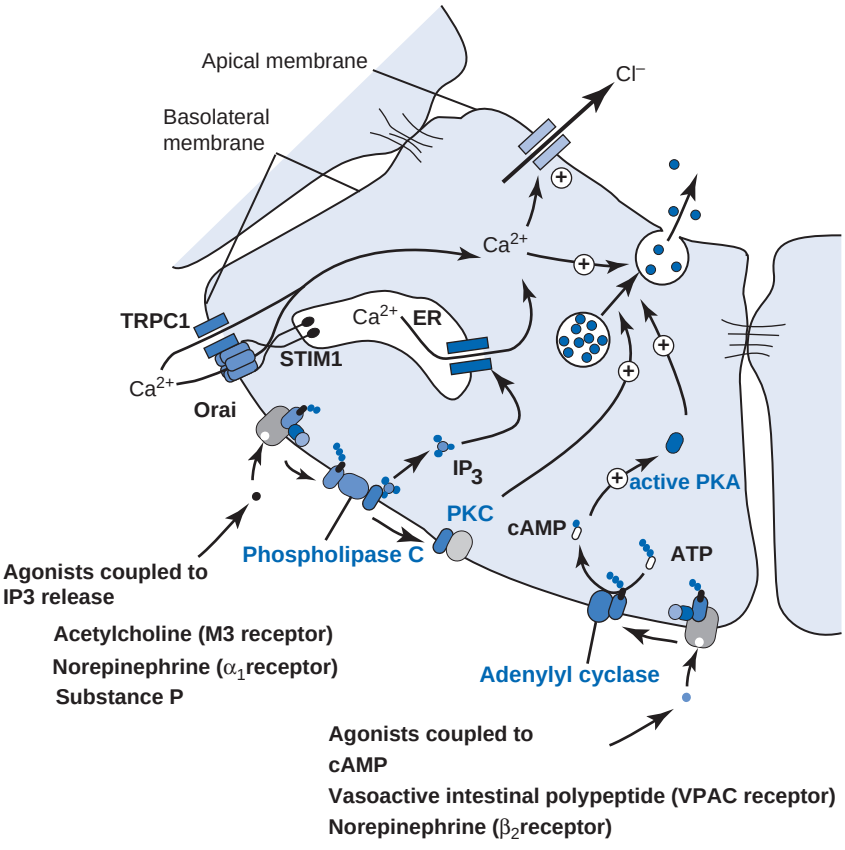

FIGURE 8.1.8 Mechanism of parasympathetic and sympathetic stimulation of salivary secretion. Parasympathetic stimulation releases acetylcholine, VIP, and Substance P in the vicinity of salivary secretory cells. The main effect is increased watery secretion mediated by acetylcholine. Acetylcholine binds to G-protein-coupled M3 receptors, whose α subunit exchanges GTP for GDP, dissociates from the $\beta\gamma$ subunits, and then activates phospholipase C. Phospholipase C then hydrolyzes membrane phosphatidyl inositol bisphosphate to produce inositol triphosphate (IP_3) and diacylglycerol. IP_3 releases Ca^{2+} from stores within the ER and increases cytosolic $[Ca^{2+}]$. The increased $[Ca^{2+}]$ activates an apical membrane Cl^- channel that powers watery secretion. Reduction in ER Ca^{2+} stores activates store-operated Ca^{2+} entry (SOCE) through STIM1, Orai, and TRPC1, and this Ca^{2+} helps prolong the stimulation. Sympathetic stimulation increases protein secretion by binding of its neurotransmitter, norepinephrine, to G-protein-coupled β_2 adrenergic receptors whose GTP-bound α subunit activates adenylyl cyclase to increase the concentration of cAMP that activates protein kinase A (PKA) to stimulate protein secretion.

blood flow allows increased salivary secretion. The net effect of decreased blood flow is increased protein content of a more viscous saliva. VIP binds to a G-protein-coupled receptor (VPAC) that activates adenylyl cyclase and increases 3′,5′ cyclic AMP within the cells. This activates protein kinase A (PKA) that stimulates protein secretion. In addition, cholinergic stimulation can increase protein secretion by means independent of cAMP, by increasing [Ca^{2+}], and activating PKC. Thus parasympathetic stimulation increases both the watery and protein secretion.

Sympathetic stimulation releases norepinephrine near the basal membranes of acinar and ductal cells. These cells are heterogeneous. Some cells possess α_1 receptors, which act through a G_q mechanism, in much the same way as M3 acetylcholine receptors, to increase the rate of production of a watery saliva. Other cells possess β_1 receptors, which act through a G_s protein to stimulate adenylyl cyclase to increase the concentration of cAMP within the cells. This results in increased protein and glycoprotein secretion. VIP also can increase cAMP. Thus the simultaneous activation of both parasympathetic and sympathetic nerves, as occurs during reflex secretion, leads to augmented secretion of salivary proteins.

IN THE FIRST STAGE OF SALIVA PRODUCTION, ACINAR CELLS SECRETE A FLUID ISOTONIC IN NaCl

Figure 8.1.9 illustrates the mechanism of fluid secretion by salivary acinar cells. The ultimate energy for the process is derived from the Na,K-ATPase located on the basolateral membranes of these cells. By pumping Na^+ out at the basolateral membrane, the pump maintains

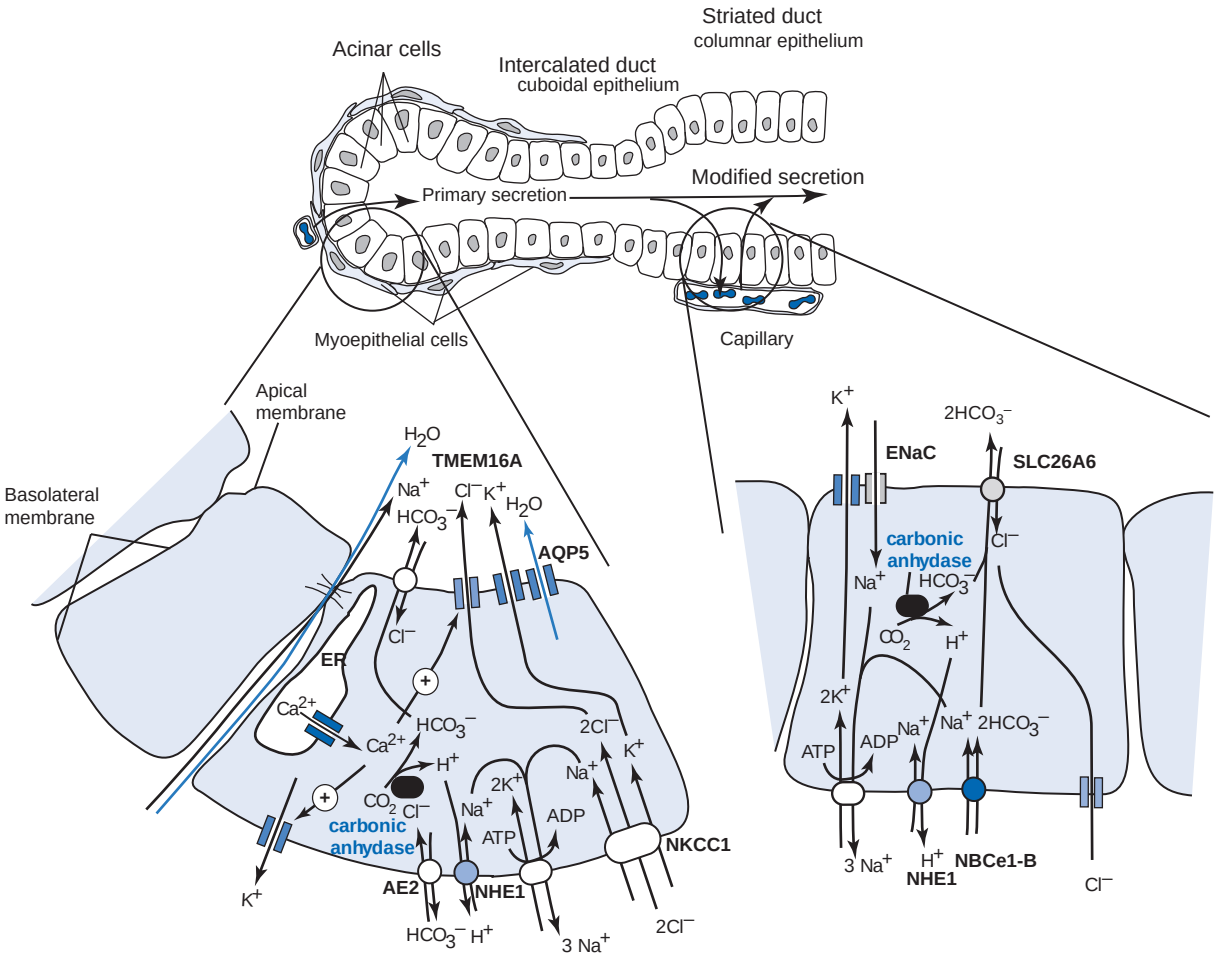

FIGURE 8.1.9 Mechanisms of salivary secretion and reabsorption. Salivary secretion takes place in two stages: the production of the primary secretion isotonic with plasma, containing mostly Na and Cl; and reabsorption of Na and Cl with secretion of K^+ and HCO_3^-. Secretion is turned on by increasing cytosolic [Ca^{2+}] through a cascade of events shown in Figure 8.1.8. The main effect of increased cytosolic [Ca^{2+}] is activation of K^+ channels at the **basolateral membrane** (the membrane lining the lateral and basal aspects of the cell, facing the blood) and Cl^- channels (**TMEM16A**) at the **apical membrane** (the membrane at the apex of the cell, facing the lumen). Cl^- efflux into the lumen and K^+ efflux into the interstitial space at the basolateral membrane create a transepithelial potential that draws Na^+ through the tight junctions. Water follows the osmotic pressure of these ions both through the tight junctions and through AQP5 in the cell. The Na,K-ATPase maintains the membrane potential and the driving forces for Na^+ entry into the cell and K^+ exit. The removal of ions shrinks the cell, turning on a Na–K–2Cl cotransporter (**NKCC1**) that further supplies ions for transport into the lumen. Because water follows passively, the saliva initially formed is isotonic with plasma. The salivary duct cells reabsorb Na^+ and Cl^- and secrete K^+ and HCO_3^-. Na^+ is reabsorbed by the **EnaC** and the Na,K-ATPase. Cl^- is reabsorbed over the apical Cl^-–$2HCO_3^-$ exchanger (**SLC26A6**) and the basolateral Cl^- channel. HCO_3^- is secreted by entry into the cell over the Na^+–$2HCO_3$ cotransporter (**NBCe1-B**) or from hydration of CO_2 by carbonic anhydrase, and then efflux from the cell over SLC26A6. The final modified secretion is hypotonic because water does not follow electrolyte reabsorption in the striated duct cells. Other transport mechanisms are present in these cells that are of lesser importance.

an inwardly directed electrochemical gradient for Na^+ and an outwardly directed electrochemical gradient for K^+. The K^+ that accumulates exits the cell by Ca^{2+}-activated channels on the basolateral membranes. The $Na^+-K^+-2Cl^-$ (**NKCC1**) cotransporter on the basolateral membrane mediates Cl^-, Na^+, and K^+ entry into the cell. The Na^+ that enters is pumped out by the Na, K-ATPase and by Na^+-H^+ exchange (**NHE1**) on the basolateral membrane. The K^+ that enters exits over Ca^{2+} activated K^+ channels. These processes lead to markedly increased $[Cl^-]$ in the cell. A second mechanism of accumulating Cl^- relies on the paired NHE1 and $Cl^- - HCO_3^-$ exchanger (**AE2**). The operation of these two brings Na^+ and Cl^- into the cell along with the net outward movement of CO_2 as $HCO_3^- + H^+$. Ca^{2+}-activated opening of Cl^- channels (**ANO1 = TMEM16A**) on the apical membrane causes a Cl^- efflux into the lumen of the acinus. Chloride entry into the lumen and K^+ exit on the basolateral side produce a transepithelial potential difference. Acinar cells have relatively leaky tight junctions that allow Na^+ to enter the lumen, along with water that moves in response to the osmotic pressure of the transported ions. Water appears to travel by both transcellular and paracellular routes. The transcellular route is through an aquaporin (AQP5). Thus the primary acinar secretion contains mainly NaCl.

IN THE SECOND STAGE OF SALIVA PRODUCTION, DUCT CELLS REABSORB NaCl AND SECRETE A HYPOTONIC $KHCO_3$

The second stage of saliva secretion occurs in the ducts (see Figure 8.1.9). At the apical membrane, Na^+ enters the ductal cell through **ENaC**, the amiloride-sensitive epithelial Na^+ channel. Na^+ that enters is pumped out of the cell by the basolateral Na,K-ATPase. Conversely, K^+ that enters the cell is secreted over an apical K^+ channel. The apical membrane contains a $Cl^- - 2HCO_3^-$ exchanger (**Slc26a6**) that secretes 2 HCO_3^- and reabsorbs 1 Cl^-. HCO_3^- enters the cell by $Na^+ - HCO_3^-$ cotransport (**NBCe1-B**) on the basolateral membrane. This minimal model can explain Na^+ and Cl^- absorption from the primary salivary secretion, and K^+ and HCO_3^- secretion into the incipient saliva.

A SWALLOWING CENTER IN THE MEDULLA ORCHESTRATES SWALLOWING

Swallowing is a tricky business because it involves passing a **bolus** of food through the pharynx into the esophagus past the trachea. One wrong move and the bolus enters the trachea and the person chokes. Further, leakage of small amounts of food into the lungs (**aspiration**) can cause potentially fatal lung problems. It is vitally important that swallowing follows a programmed series of events every time we swallow. The sequence of events is controlled by a **swallowing center** located in the **medulla** in or near the nucleus of the solitary tract (NST). This center receives sensory input from the mouth and pharynx and delivers efferent motor commands via the trigeminal (CN V), facial (CN VII), and hypoglossal (CN IX) nerves.

SWALLOWING IS A COMPLEX SEQUENCE OF EVENTS

Swallowing is initiated voluntarily by actions of the tongue on material in the mouth. Sensors within the mucosa of the mouth inform the brain of the size and physical characteristics of the food. Unlike other animals we generally cannot swallow large chunks of food. When the food is sufficiently broken down, the tongue separates the food into the part to be swallowed by pressing the tip of the tongue against the **soft palate**. The tongue then elevates and retracts against the palate, pushing the bolus of food back toward the **pharynx**, the topmost part of the throat. The sequence of events in swallowing is illustrated in Figure 8.1.10.

Although the swallowing reflex can begin voluntarily, it cannot be sustained without sensory input from fluid or matter on sensory receptors that line the pharynx. Afferent sensory information travels over the trigeminal (CN V), vagus (CN X), and glossopharyngeal (CN IX) nerves to the swallowing center, which then coordinates swallowing through efferent nerves. This programmed sequence, once initiated, cannot be easily stopped. Blockade of sensory information by local anesthesia, for example, interferes with the proper coordination of swallowing and may result in aspiration. Thus the proper coordination of swallowing requires sensory feedback from mechanosensors distributed throughout the pharynx and larynx.

SWALLOWING CONSISTS OF A *PHARYNGEAL PHASE* AND AN *ESOPHAGEAL PHASE*

The process of swallowing described in Figure 8.1.10 refers to the **pharyngeal phase** of swallowing that encompasses movement of food or liquids from the mouth past the upper esophageal sphincter. In the **esophageal phase**, food is propelled down the esophagus by smooth muscle contraction. The wave of muscular contraction that immediately follows the pharyngeal phase is called **primary peristalsis**. It is a programmed event that is controlled by neural efferents from the swallowing center. The esophagus is highly unusual in that the uppermost 5–10% of the esophagus consists of striated skeletal muscle. The lower 50% is entirely smooth muscle, whereas the middle 30–40% is a mixture of both striated and smooth muscles. Thus the vagus efferent from the swallowing center controls a skeletal muscle in the upper esophagus. The vagus sequentially activates the skeletal muscle portion and the smooth muscle portion in a seamless, coordinated manner to produce smooth movement of the food to the stomach.

Generally primary peristalsis successfully clears the esophagus of the bolus and the food or liquid enters the stomach. Food remaining in the esophagus following primary peristalsis stretches the esophagus, and mechanoreceptors in the esophagus sense this stretch.

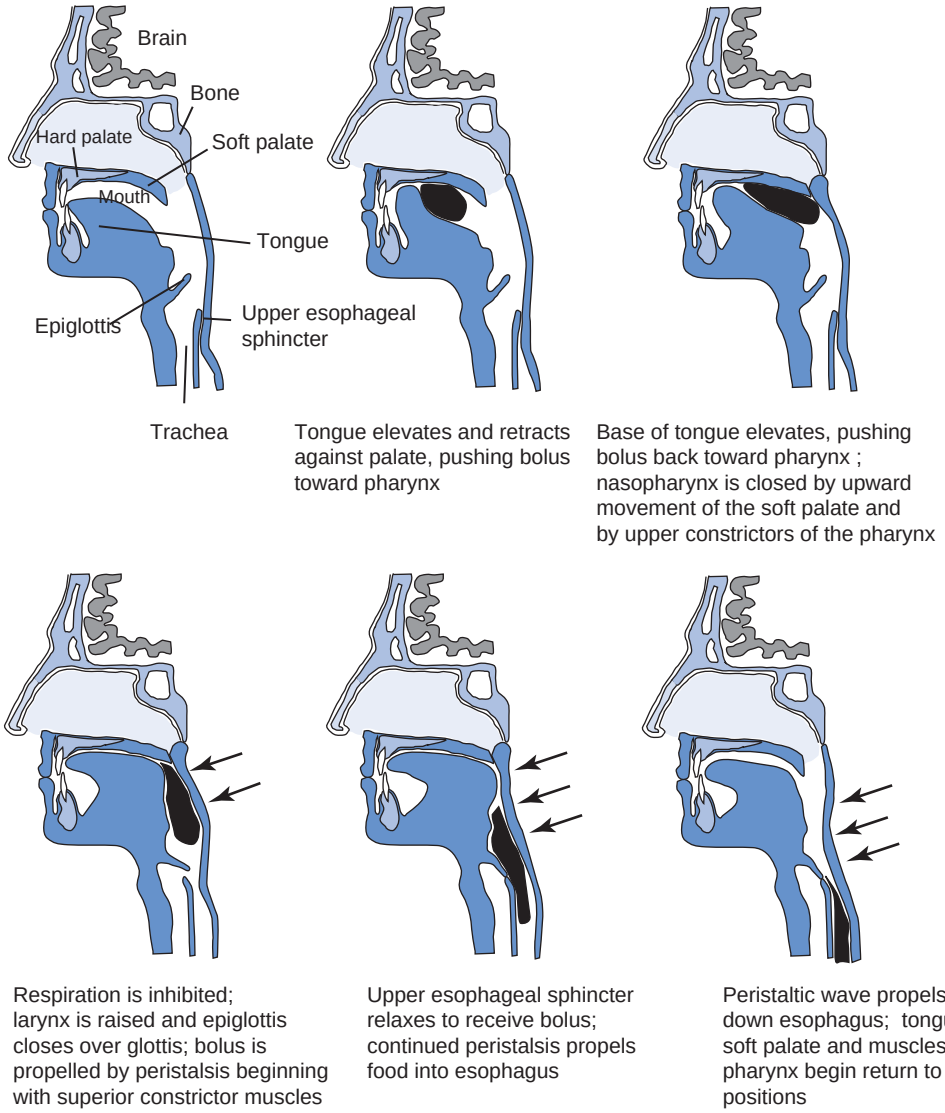

FIGURE 8.1.10 Sequential events in swallowing. Swallowing is initiated by voluntarily pushing a bolus of food toward the pharynx by elevating the tongue against the soft palate. The nasopharynx closes by apposition of the soft palate with the upper constrictor muscles of the pharynx. The tongue continues to push the food back into the pharynx. This initiates a sequential constriction of the muscles of the pharynx in a wave of contraction called peristalsis. This moves the food down into the larynx. Respiration is inhibited, the larynx is elevated, and the **epiglottis** closes over the glottis to prevent aspiration of food or fluid into the lungs. The peristaltic wave pushes the food down toward the esophagus, while the **upper esophageal sphincter** opens to accept it.

The stretch receptors directly affect smooth muscle contraction by actions on interneurons contained within the esophagus itself and by afferent input to the swallowing center to activate **secondary peristalsis** (see Figure 8.1.11). Secondary peristalsis is a **vagovagal reflex** because both the sensory and motor travels over the vagus nerve.

THE ESOPHAGUS CONTAINS AN INNER CIRCULAR SMOOTH MUSCLE LAYER AND AN OUTER LONGITUDINAL SMOOTH MUSCLE LAYER

Epithelial cells make up the **mucosa** that lines the lumen of the esophagus. Immediately below the mucosa is a layer of smooth muscle called the **muscularis mucosae**. Below the muscularis mucosa is a layer of **submucosa** containing blood vessels, connective tissue, and immunological cells such as macrophages. Below the submucosa (toward the outside of the esophagus) are two other layers of muscle, generally thicker and more developed than the thin muscularis mucosa. The layer closest to the lumen consists of cells oriented circumferentially. This is the **circular muscle** layer. Contraction of these cells constricts the tube. Outside the circular layer is another layer of smooth muscle oriented longitudinally, the **longitudinal muscle**. This controls the length of the tube. This layered organization of the esophagus is similar to that of the entire GI tract (see Figure 8.1.12).

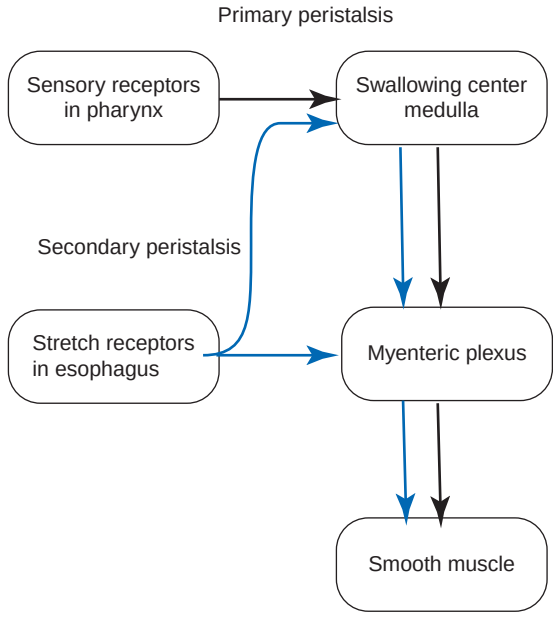

FIGURE 8.1.11 Block diagram of the control of primary and secondary peristalsis. Primary peristalsis arises as part of the programmed sequence of events initiated by the swallowing center. Secondary peristalsis arises from sensory input from stretch receptors within the esophagus that communicates both with the myenteric plexus in the esophagus and with the swallowing center. Both the sensory arm and the efferent arm of secondary peristalsis travel over the vagus nerve, and so this reflex is a **vagovagal reflex**.

THE GUT CONTAINS TWO GANGLIONIC PLEXUSES OF NERVE CELLS, THE BODY'S "LITTLE BRAIN"

In the intestine, nerve cells are collected into small groups in between the outer longitudinal muscle layer and the inner circular muscle layer. These bunches of nerve cells collectively form the **myenteric plexus**. These nerve cells receive local sensory input from the GI tract and respond to central efferent commands. Each group of neurons communicates with others up and down the GI tract. The arrangement of muscle layers and nerves and their control is illustrated in Figure 8.1.12. Underneath the circular muscular layer is a second nerve plexus, the **submucosal plexus**. It contains sensory neurons that detect stimuli from the lumen of the GI tract, and secretomotor cells that control secretion and contraction of the inner circular layer and the **muscularis mucosa**.

THE *LES* MUST RELAX FOR FOOD TO ENTER THE STOMACH

The lower esophageal sphincter (LES) tonically constricts the opening between the stomach and the esophagus. This prevents reflux of acidic stomach contents into the esophagus, which is poorly equipped to deal with it. Peristalsis of the esophagus is generally followed by relaxation of the LES and entry of food into the stomach. The vagus nerve relaxes the LES through the release of **VIP** and **nitric oxide (NO)**.

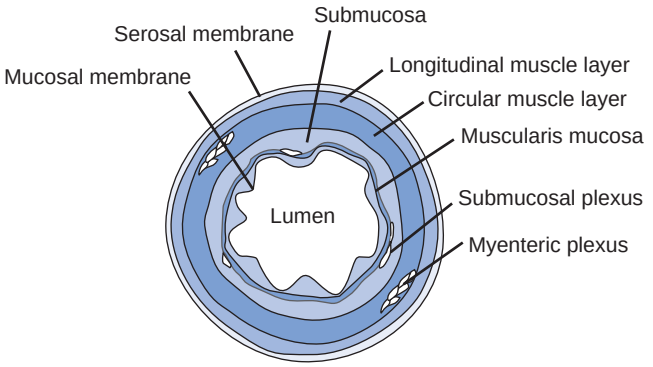

FIGURE 8.1.12 Cross-section of the esophagus showing the innermost lining of the lumen, the mucosal membrane, and its underlying structures. The muscularis mucosa is a thin layer of muscle whose contraction folds the mucosa to form ridges and valleys. Below the muscularis mucosa is the submucosa containing connective tissue, blood vessels, and nerves. The nerve complex here is the submucosal plexus. Further outward is an inner circular layer and an outer longitudinal layer. Between them is another interconnected nerve network called the myenteric plexus. These nerve plexuses control GI motility and secretion.

SUMMARY

The function of the GI tract is to extract nutrients from the ingested food to provide building blocks for our bodies and energy to power its movement and metabolism. The GI tract is basically a tube that runs from mouth to anus. The tube has specialized areas that are separated by muscular sphincters that control the movement of material from one part to the next. The esophagus brings food to the stomach, which stores it and reduces its particle size. The esophagus is marked by an upper esophageal sphincter and a lower esophageal sphincter. The pyloric sphincter controls stomach emptying into the small intestine, which consists of the duodenum, jejunum, and ileum. The ileocecal sphincter controls movement of the luminal contents into the large intestine, which consists of the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon. The sigmoid colon connects to the rectum. Defecation is controlled by two sphincters, the internal and external anal sphincters.

Digestion begins in the mouth where food is chewed and mixed with saliva. Chewing decreases particle size, increases the surface area, breaks down vegetable cell walls, mixes the food with saliva and other foods, and moves it around so it may be sampled.

Saliva moistens and lubricates the food, buffers the mouth pH, helps ward off infections, and helps heal the esophagus. In addition, it facilitates speech by keeping the mouth moist. Saliva is formed in acinar (grape shaped) glands in the parotid, submandibular, and sublingual glands. The parotid gland produces only fluid, whereas the submandibular and sublingual glands add mucin, glycoproteins that help lubricate food, and other proteins. The fluid flows down an intercalated duct to reach a striated duct, which modifies the saliva by reabsorbing ions. Saliva as formed is isotonic with plasma,

Clinical Applications: Achalasia

Achalasia is a disorder of esophageal motility which interferes with food passing from the esophagus to the stomach. It is characterized by increased LES pressure, diminished peristalsis in the distal third of the esophagus, and lack of coordinated relaxation of the LES in response to primary or secondary peristalsis in the esophagus. Sir Thomas Willis first described the condition in 1674, and he successfully treated his patient by dilating the LES with a cork-tipped whalebone. The condition is relatively rare, with an incidence of four to six cases per million persons and a prevalence of eight cases per million. Its etiology is unknown. Current theories of causality include autoimmune disorders and infection. Commonly, the myenteric plexus (Auerbach's plexus) degenerates, with death of inhibitory neurons that secrete **VIP** and **NO**. Both of these neurotransmitters inhibit GI motility and cause relaxation of sphincters (see Chapter 8.3).

Failure to relax the LES causes entrapment of food in the esophagus with subsequent enlargement of the esophagus (megaesophagus). This inflames and irritates the esophagus (**esophagitis**). The trapped food causes regurgitation, which in turn can cause nocturnal coughing and aspiration. Aspiration of esophageal contents leads to pneumonia and lung abscesses.

Achalasia can be diagnosed by **video esophagraphy** in which the patient swallows a radio-opaque solution (barium) during fluoroscopy. The barium absorbs X-rays and therefore it shows the enlarged end of the esophagus and a narrow tapering at the sphincter. In persons with achalasia, the barium solution empties into the stomach more slowly. This test must be confirmed by endoscopic examination and esophageal manometry. **Esophageal manometry** is the standard criterion for diagnosis of the disease. Esophageal manometry measures the pressures in the esophagus by passing a thin tube into the esophagus. In persons with achalasia, there is no pressure wave in the distal esophagus following a swallow, and the pressure within the contracted sphincter does not decrease with the swallow.

There are several treatment options for achalasia, including oral medications, dilation of the sphincter by a balloon placed within the esophagus, surgical cutting of the muscle (myotomy), and botox injection. The oral medications consist of four distinct classes, all of which aim to relax smooth muscle. The goal of LES dilation and surgery is to tear or cut the muscle fibers to reduce the restriction of food entering the stomach.

Injection of botulinum toxin (botox) into the LES relaxes the sphincter by a complicated mechanism. *Clostridium botulinum* is a gram-negative bacterium that produces seven related toxins, called botulinum toxin types A, B, C1, D, E, F, and G. The toxin is synthesized as a protoxin of 150 kDa, which is subsequently cleaved to light (L) and heavy (H) chains that remain linked by a disulfide bond. Nerve terminals have receptors for both the H- and L-chains. The L-chain is transported across the nerve terminal membrane by endocytosis, and it becomes incorporated into endosomes. The various L-chains are **metalloproteinases**—proteases that require metal ions for activity. The L-chains bind Zn^{2+}. Their substrates are one of several proteins that make up the **SNARE** complex that is required for neurotransmitter vesicle fusion with the presynaptic nerve membrane. At least three proteins are involved in this process: v-SNARE (synaptobrevin) is associated with neurotransmitter vesicles; t-SNARE (syntaxin) is on the presynaptic membrane; and SNAP-25, another t-SNARE. All of these proteins are required for the docking of vesicles in the active zone of the presynaptic terminal and for subsequent neurotransmission. Each of the botulinum toxins cleaves one of these three proteins and thereby interferes with neurotransmitter release. Thus botulinum toxin causes paralysis of the muscles. Injection of botulinum toxin into the LES thus causes its relaxation and improves emptying of food into the stomach.

Clinical Applications: GERD and Hiatal Hernia

The Clinical Applications box about achalasia details the condition, complications, diagnosis, and treatment for the situation when the LES does not relax coordinately with esophageal peristalsis. Gastroesophageal reflux disease, or GERD, is its opposite: the LES does not constrict enough to adequately retain stomach contents within the stomach. The result is that the stomach contents **reflux** into the esophagus. The acidic stomach contents causes a burning sensation in the throat or chest which is colloquially called **heartburn**. However, gastroesophageal reflux may be asymptomatic. Persistent heartburn more than twice weekly may be considered to indicate GERD.

The cause of the condition is unknown. Anyone can have GERD, including infants and children. Obesity is a risk factor and losing weight is one of the lifestyle changes recommended for persons with GERD. Hiatal hernia is also a risk factor. However, the majority of persons with hiatal hernias are asymptomatic, and many persons with GERD do not have hiatal hernia.

The esophagus is approximately 30 cm long, passing from pharynx to stomach. The diaphragm forms a dome that separates the thoracic cavity from the abdominal cavity. Contraction of the diaphragm expands the thoracic cavity, reducing the pressure of the gas in the lungs. This causes air to move into the lungs, and so contraction of the diaphragm drives inhalation. To do this, the diaphragm must seal off the two cavities. To reach the stomach, the esophagus must pass through the diaphragm. Thus there is a hole in the diaphragm to allow the esophagus to pass through. This is the **hiatus**. The diaphragm is sealed around the esophagus by the phrenoesophageal ligament. This fibrous layer of connective tissue not only seals the hiatus but anchors the esophagus so that the LES lies within the abdominal cavity and not the thorax. Sometimes the LES anchor gives way and the LES moves upward through the diaphragm into the thorax. This is a hiatal hernia. The lower pressure within the thorax is transmitted to the esophagus, which thereby loses some of its effectiveness as a sphincter.

The esophagus lacks protection against luminal acid, and so it may be damaged by acid reflux. The damage may cause bleeding. Esophageal ulcers and scars that develop may narrow the esophagus, making swallowing difficult. Some people develop **Barrett's esophagus**, in which the cells lining the esophagus become more like intestinal cells. It is generally regarded as being a precancerous condition.

but reabsorption of ions produces a hypotonic saliva. Slow flow allows the striated duct cells more time to reabsorb ions, so the osmolarity decreases as the flow decreases. Both parasympathetic and sympathetic nerves influence saliva production. Parasympathetic stimulation increases serous saliva (without protein), whereas sympathetic stimulation increases protein secretion. The salivary nuclei in the medulla control salivation. Smell, taste, and feel of food in the mouth, as well as just thinking about food, all promote salivation. Fatigue, dehydration, fear, and sleep all depress salivation.

Swallowing is a tricky business because you have to avoid getting material in the trachea. The mechanism for swallowing is hard wired before birth and does not require learning. The swallowing center in the medulla uses sensory information provided by the trigeminal (cranial nerve V), glossopharyngeal (cranial nerve IX), and vagus (cranial nerve X) to determine when food is ready to be swallowed. The swallowing program is initiated voluntarily but cannot be interrupted voluntarily. The swallowing program sequentially pushes the food backward toward the pharynx, closes the nasopharynx, constricts the pharynx, lifts the larynx and blocks the glottis with the epiglottis, and relaxes the upper esophageal sphincter. Primary peristalsis is a wave of contraction of the esophagus that immediately follows swallowing. It usually sweeps the swallowed food bolus into the stomach. If food remains in the esophagus, it stretches the esophagus and begins a secondary peristalsis.

The upper part of the esophagus is striated muscle like skeletal muscle though it is not connected to bone. The middle part is a mixture of striated and smooth muscles, whereas the part near the stomach is smooth muscle. The basic structure of the esophagus is like that of the rest of the GI tract: the lumen of the intestine is lined with an epithelial mucosa. The submucosa contains the muscularis mucosa that folds the mucosa, the submucosal plexus, blood vessels, and glands. Further outward is the circular muscle layer and the longitudinal muscle layer. The circular muscle determines the caliber of the tube and the longitudinal muscle controls its length. Between them is the myenteric plexus of nerves that responds to local sensory stimulation and to commands from the autonomic nervous system.

REVIEW QUESTIONS

1. What is a sphincter? Name the GI sphincters, in order, from mouth to anus.
2. What is mucus? What does it do? What salivary glands produce it? What stimulates its production?
3. How does parasympathetic stimulation stimulate serous saliva production?
4. Why is swallowing so complicated? What controls swallowing? What would happen if that area is damaged by a stroke, for example?
5. What is peristalsis? In the esophagus, what causes primary peristalsis? What causes secondary peristalsis? What is a vagovagal reflex?
6. What muscle layers are responsible for peristalsis? What controls these muscle layers?