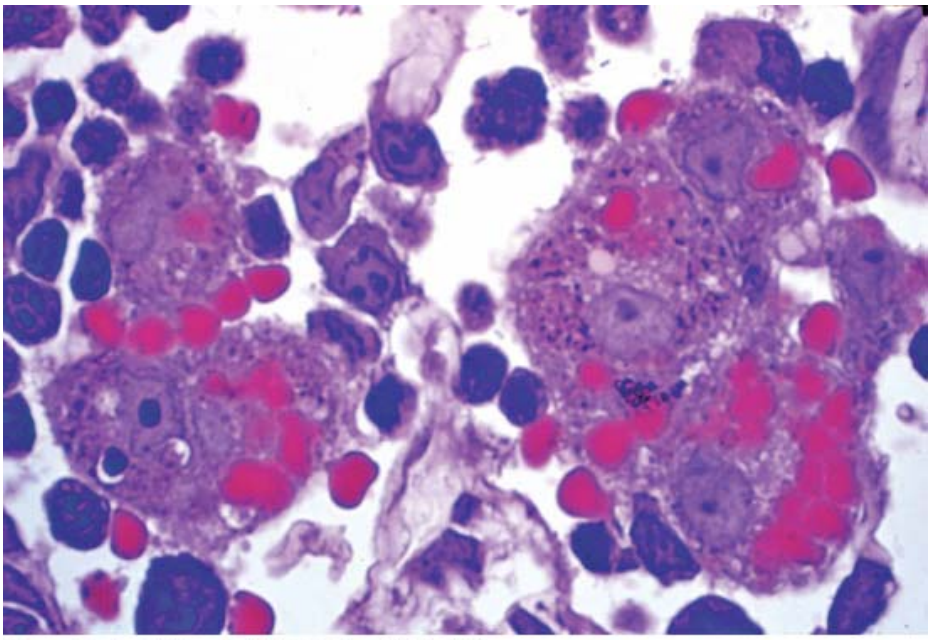


Erythrocyte removal by splenic macrophages.

A micrograph of five macrophages in a splenic cord shows active phagocytosis of effete erythrocytes. After about 120 days of use erythrocytes undergo membrane changes and swell, signals for their engulfment by macrophages in the cords of reticular tissue between the venous sinuses. Healthy, flexible erythrocytes are pushed between stave cells and enter the sinuses. Phagocytosed erythrocytes are completely degraded within lysosomes. The iron released from hemoglobin binds its transport protein transferrin, returns to the circulation, and is reused primarily for erythropoiesis in bone marrow. Iron-free heme either binds its transport protein, hemopexin, or is metabolized to bilirubin and excreted in the bile by liver cells. After surgical removal of the spleen (splenectomy) the number of abnormal erythrocytes in the circulation increases, although many such cells are now removed in the bone marrow and liver. X400. PT.

MEDICAL APPLICATION

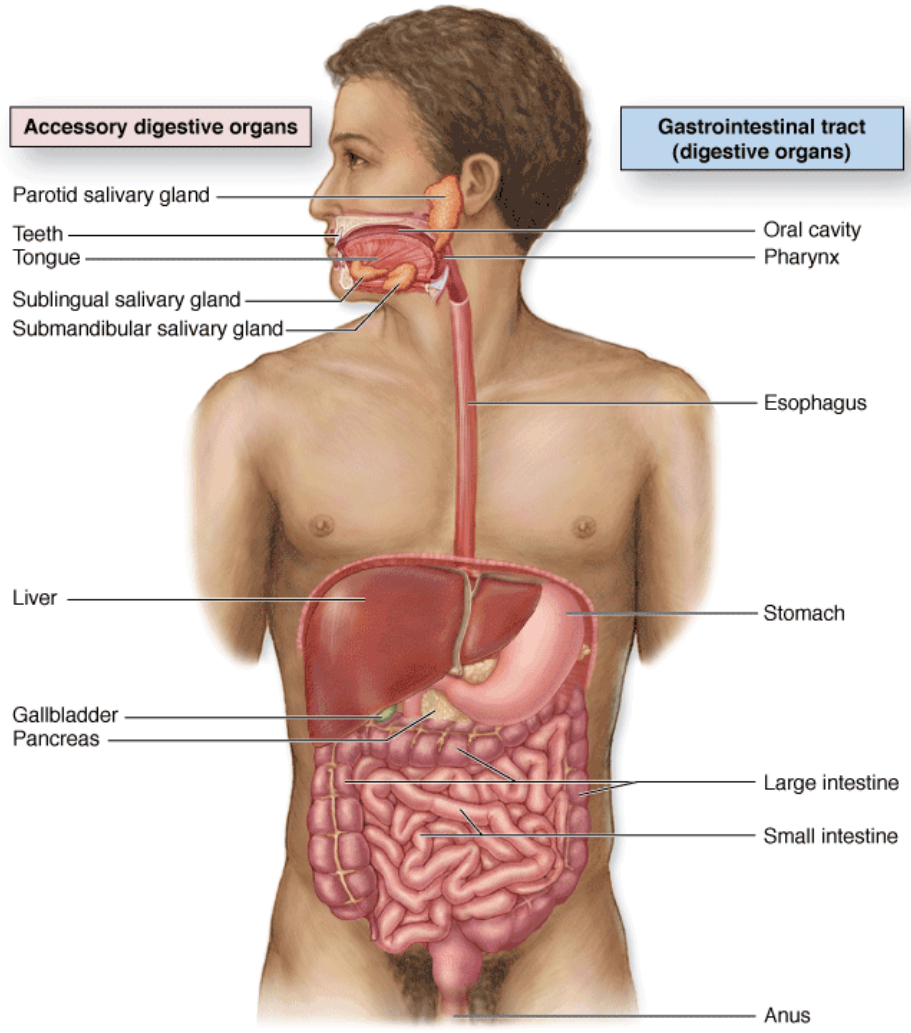
Although the spleen has numerous important functions in the body, it is not essential to life. In some situations the spleen must be removed (eg, an abdominal injury that results in rupture of the spleen capsule, certain anemias, and platelet disorders). In this case other organs such as the liver and bone marrow can take over many of the functions of the spleen, although the risk of infection may be higher in a splenectomized individual.

Note: Large images and tables on this page may necessitate printing in landscape mode.

DIGESTIVE TRACT: INTRODUCTION

The digestive system consists of the digestive tract—oral cavity, esophagus, stomach, small and large intestines, rectum, and anus—and its associated glands—salivary glands, liver, and pancreas (Figure 15–1). Its function is to obtain from ingested food the molecules necessary for the maintenance, growth, and energy needs of the body. Macromolecules such as proteins, fats, complex carbohydrates, and nucleic acids are broken down into small molecules that are more easily absorbed through the lining of the digestive tract, mostly in the small intestine. Water, vitamins, and minerals from ingested food are also absorbed. In addition, the inner layer of the digestive tract is a protective barrier between the content of the tract's lumen and the internal milieu of the body.

Figure 15–1.



Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

The digestive system.

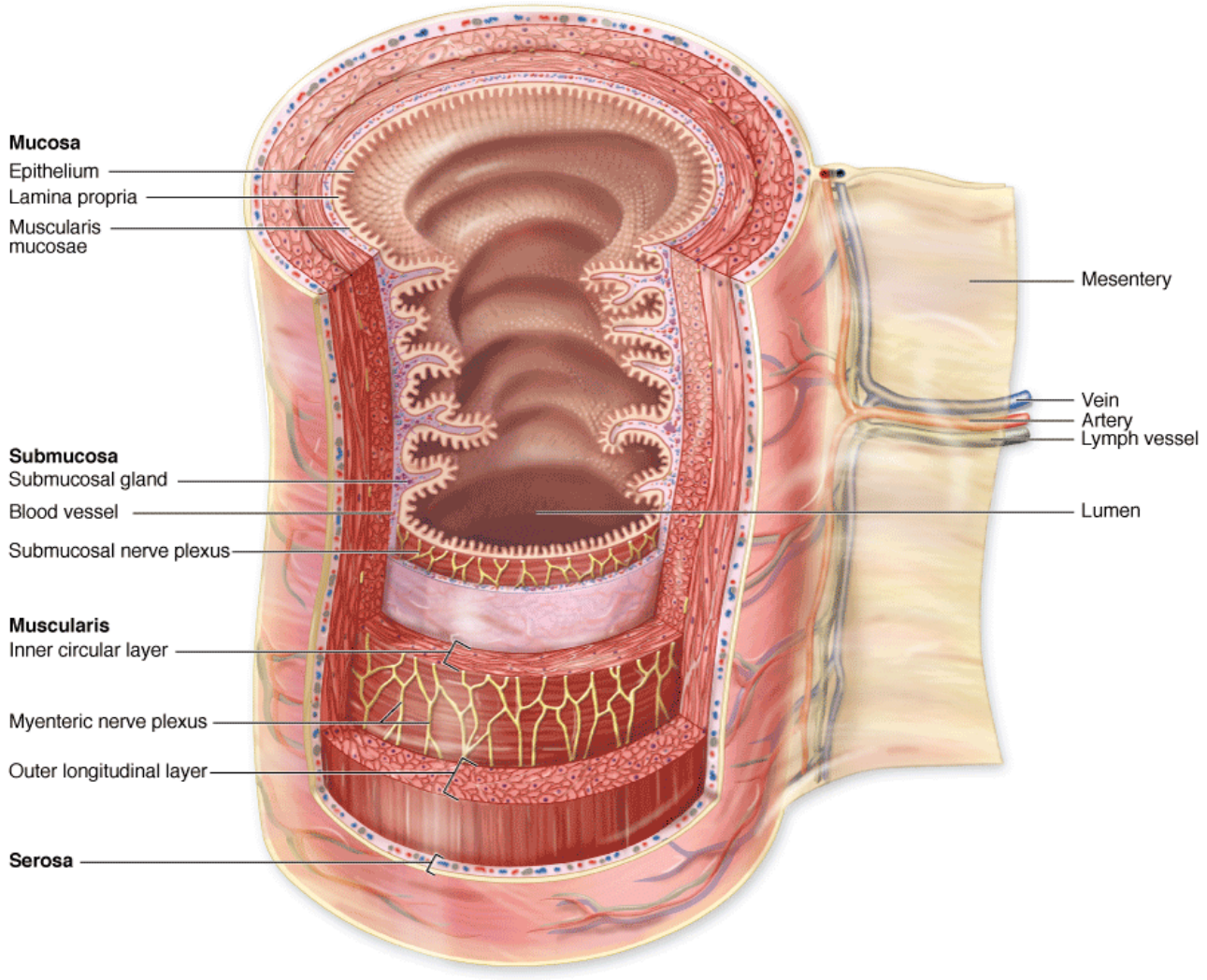
The digestive system consists of the tract from the mouth (oral cavity) to the anus, as well as the digestive glands emptying into this tract, primarily the salivary glands, liver, and pancreas. These accessory digestive glands are described in the next chapter.

The first step in digestion occurs in the mouth, where food is moistened by saliva and ground by the teeth into smaller pieces; saliva also initiates the breakdown of carbohydrates. Digestion continues in the stomach and small intestine, where the food's basic components (eg, amino acids, monosaccharides, free fatty acids) are absorbed. Water absorption occurs in the large intestine, causing undigested material to become semisolid.

GENERAL STRUCTURE OF THE DIGESTIVE TRACT

The entire gastrointestinal tract has certain common structural characteristics. It is a hollow tube with a lumen of variable diameter and a wall made up of four main layers: the **mucosa, submucosa, muscularis,** and **serosa.** The structure of these layers is summarized below and is illustrated for the small intestine in Figure 15–2.

Figure 15–2.



Major layers and organization of the digestive tract.

Schematic diagram showing the structure of the small intestine portion of the digestive tract, with the four layers and their major components listed on the left. The intestines are suspended by mesenteries which are the sites of blood vessels and lymphatics from the intestines.

The **mucosa** comprises an **epithelial lining;** an underlying **lamina propria** of loose connective tissue rich in blood vessels, lymphatics, lymphocytes and smooth muscle cells, sometimes also containing glands; and a thin layer of smooth muscle called the **muscularis mucosae** usually separating mucosa from submucosa. The mucosa is frequently called a **mucous membrane.**

The **submucosa** contains denser connective tissue with many blood and lymph vessels and the **submucosal plexus** of autonomic nerves. It may also contain glands and lymphoid tissue.

The thick **muscularis** is composed of smooth muscle cells that are spirally oriented and divided into two sublayers. In the internal sublayer (closer to the lumen), the orientation is generally circular; in the external sublayer, it is mostly longitudinal. In the connective tissue between the muscle sublayers are blood and lymph vessels, as well as another autonomic **myenteric nerve plexus**. This and the submucosal plexus together comprise the local **enteric nervous system** of the digestive tract, containing largely autonomic neurons functioning independently of the central nervous system (CNS).

The **serosa** is a thin layer of loose connective tissue, rich in blood vessels, lymphatics, and adipose tissue, with a simple squamous covering epithelium (**mesothelium**). In the abdominal cavity, the serosa is continuous with the mesenteries (thin membranes covered by mesothelium on both sides), which support the intestines, and with the peritoneum, a serous membrane that lines the cavity. In places where the digestive tract is not suspended in a cavity but bound to other structures, such as in the esophagus (Figure 15–1), the serosa is replaced by a thick **adventitia**, consisting of connective tissue containing vessels and nerves, lacking mesothelium.

The main functions of the digestive tract's epithelial lining are to:

- Provide a selectively permeable barrier between the contents of the tract and the tissues of the body,
- Facilitate the transport and digestion of food,
- Promote the absorption of the products of this digestion,
- Produce hormones that affect the activity of the digestive system,
- Produce mucus for lubrication and protection.

The abundant lymphoid nodules in the lamina propria and the submucosal layer protect the organism (in association with the epithelium) from bacterial invasion, as described in Chapter 14. The necessity for this immunologic support is obvious, because the entire digestive tract—with the exception of the oral cavity, esophagus, and anal canal—is lined by a simple thin, vulnerable epithelium. The lamina propria, located just below the epithelium, is a zone rich in macrophages and lymphocytes, some of which actively produce antibodies. These antibodies are mainly immunoglobulin A (IgA) and are secreted into the intestinal lumen bound to a secretory protein produced by the epithelial cells. This complex protects against viral and bacterial invasion. IgA is

resistant to proteolytic enzymes and can therefore coexist with the proteases present in the lumen.

The muscularis mucosae allows local movements of the mucosa independent of other movements of the digestive tract, increasing contact of the lining with food. The contractions of the muscularis, generated and coordinated by autonomic nerve plexuses, propel and mix the food in the digestive tract. These plexuses are composed mainly of nerve cell aggregates (multipolar visceral neurons) that form small parasympathetic ganglia. A rich network of pre- and postganglionic fibers of the autonomic nervous system and some visceral sensory fibers in these ganglia permit communication between them. The number of these ganglia along the digestive tract is variable; they are most numerous in the regions of greatest motility.

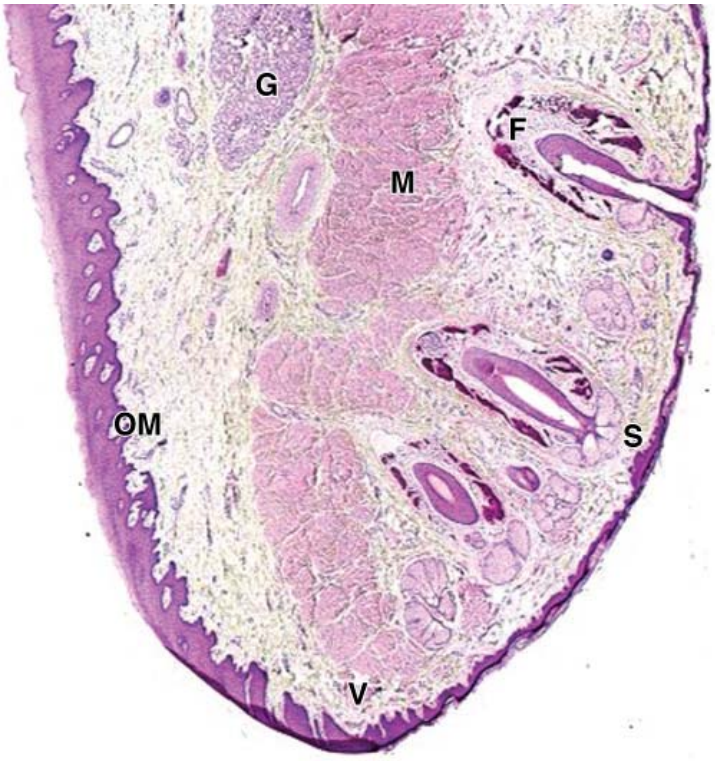
MEDICAL APPLICATION

In certain diseases, such as **Hirschsprung disease** (congenital megacolon) or **Chagas disease** (**Trypanosoma cruzi** infection), the plexuses in the digestive tract are severely injured and most of their neurons are destroyed. This results in disturbances of digestive tract motility, with frequent dilatations in some areas. The abundant innervation from the autonomic nervous system that the digestive tract receives provides an anatomic explanation of the widely observed action of emotional stress on this tract.

ORAL CAVITY

The oral cavity (Figure 15–1) is lined with stratified squamous epithelium, keratinized or nonkeratinized, depending on the region. The keratin layer protects the oral mucosa from damage during masticatory function and is best developed on the gingiva (gum) and hard palate. The lamina propria in these regions has many papillae and rests directly on bony tissue. Nonkeratinized squamous epithelium covers the soft palate, lips, cheeks, and the floor of the mouth. Surface cells are shed continuously and replaced by progeny of stem cells in the basal epithelial layer. The lamina propria has papillae similar to those in the dermis of the skin and is continuous with a submucosa containing diffuse small salivary glands. The soft palate also has a core of skeletal muscle and lymphoid nodules. In the **lips**, there is also striated muscle and a transition from the oral nonkeratinized epithelium to the keratinized epithelium of the skin (Figure 15–3).

Figure 15–3.



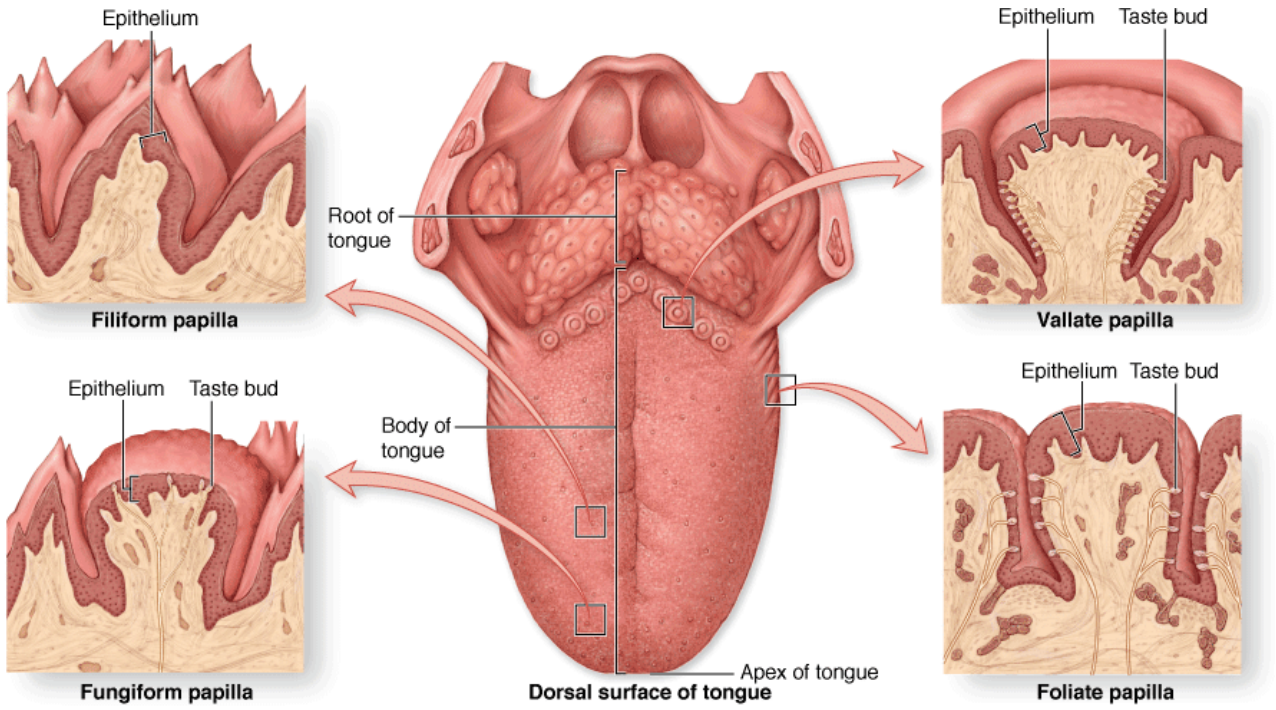
Lip.

Low-magnification micrograph of a lip section showing one side covered by typical **oral mucosa** (OM), the opposite side covered by skin (S) containing hair follicles (F) and associated glands. Between the oral portion of the lips and normal skin is the vermilion (V), or the vermilion zone, where epidermis is very thin, lightly keratinized, and transparent to blood in the rich microvasculature of the underlying connective tissue. Because this region lacks the glands for oil and sweat, it is prone to excessive dryness and chapping in cold, dry weather. Internally, the lips contain much-striated muscle (M) and many minor salivary glands (G). X10. H&E.

Tongue

The tongue is a mass of striated muscle covered by a mucous membrane whose structure varies according to the region. The muscle fibers cross one another in three planes and are grouped in bundles separated by connective tissue. Because the connective tissue of the lamina propria penetrates the spaces between the muscular bundles, the mucous membrane is strongly adherent to the muscle. The mucous membrane is smooth on the lower surface of the tongue. The tongue's dorsal surface is irregular, covered anteriorly by a great number of small eminences called **papillae.** The posterior third of the tongue's dorsal surface is separated from the anterior two thirds by a V-shaped groove, the **terminal sulcus**. Behind this boundary is the root of the tongue, whose surface shows the many bulges of the lingual tonsils and smaller collections of lymphoid nodules (Figure 15–4).

Figure 15–4.



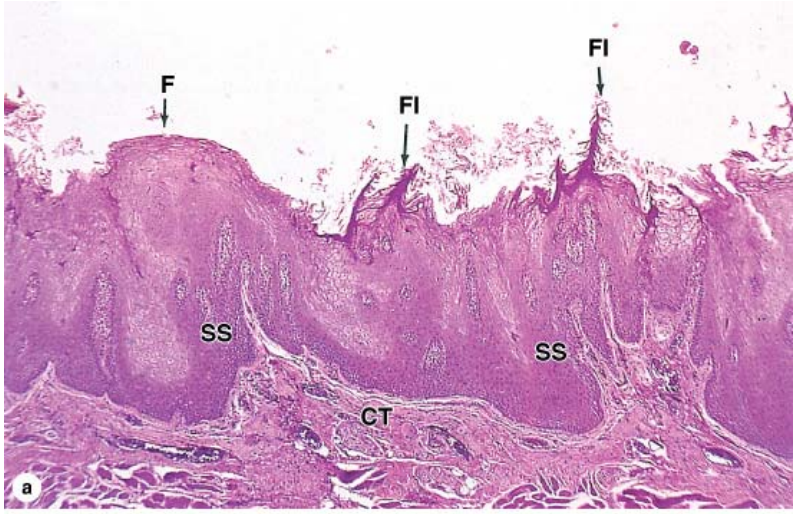
Tongue and lingual papillae.

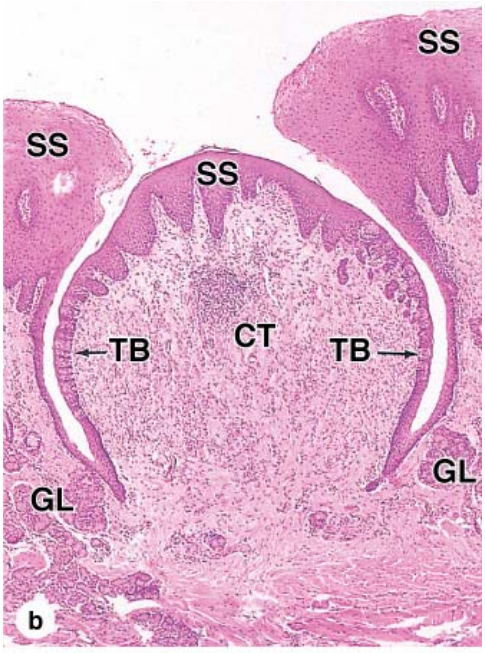
The posterior third of the tongue is the root and the anterior two-thirds the body of the tongue. The mucosa of the root is filled with masses of lymphoid nodules separated by crypts, all of which comprise the lingual tonsils. On the body of the tongue are papillae of four types, all containing cores of connective tissue covered by stratified squamous epithelium. Pointed filiform papillae provide friction to help move food during chewing. Ridge-like foliate papillae on the sides of the tongue are best-developed in young children. Fungiform papillae are scattered across the dorsal surface and 6-12 very large vallate papillae are present in a V-shaped line near the terminal sulcus. Taste buds are present on fungiform and foliate papillae but are much more abundant on vallate papillae.

The numerous papillae on the anterior portion of the tongue are elevations of the mucous membrane that assume various forms and functions. Four types are recognized (Figure 15–4):

- **Filiform papillae** (Figure 15–5) are very numerous, have an elongated conical shape, and are heavily keratinized, which gives their surface a gray or whitish appearance. Their epithelium lacks taste buds (described below) and their role is mechanical in providing a rough surface that facilitates food movement during chewing.
- **Fungiform papillae** (Figure 15–5) are less numerous, lightly keratinized, and mushroom-shaped with connective tissue cores and scattered taste buds on their upper surfaces. They are irregularly interspersed among the filiform papillae.
- **Foliate papillae** are poorly developed in adults, but consist of parallel ridges and furrows on the sides of the tongue, with taste buds.
- **Vallate** (or circumvallate) **papillae** (Figure 15–5) are the least numerous and largest lingual papillae, and have over half the taste buds on the human tongue. With diameters of one to three mm, seven to twelve circular vallate papillae normally form a V-shaped line just before the terminal sulcus. Ducts from several serous salivary (von Ebner) glands empty into the deep groove that surrounds each vallate papilla. This moatlike arrangement provides a continuous flow of fluid over the taste buds abundant on the sides of these papillae, which washes food particles from the vicinity so that the taste buds can receive and process new gustatory stimuli. These glands also secrete a lipase that prevents the formation of a hydrophobic film over the taste buds that would hinder their function.

Figure 15–5.





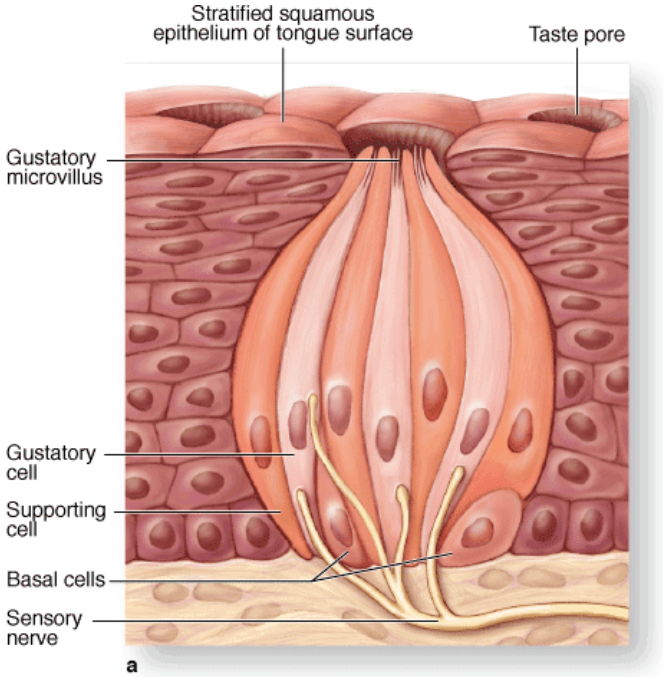
Lingual papillae.

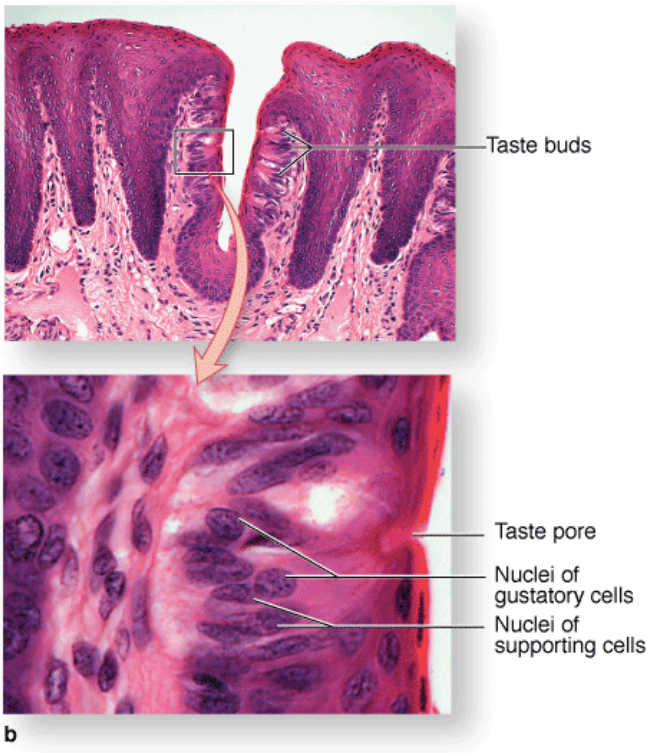
(a): Section of the dorsal surface of tongue shows both filiform (FI) and fungiform papillae (F). Both types are elevations of the connective tissue (CT) covered by stratified squamous epithelium (SS), but the filiform type is pointed and heavily keratinized while the fungiform type is mushroom-shaped, lightly keratinized, and has a few taste buds. **(b):** Micrograph shows a single very large vallate papilla with two distinctive features: many taste buds (TB) around the sides and several small salivary glands (GL) emptying into the cleft or moat formed by the elevated mucosa surrounding the papilla. These glands continuously flush the cleft, renewing the fluid in contact with the taste buds. The 7 to 12 vallate papillae on the tongue contain over half of the 10,000 or so taste buds in the human mouth and pharynx. Both X20. H&E.

Taste buds are also present in other parts of the oral cavity, such as the soft palate, and are continuously flushed by numerous small salivary glands dispersed throughout the oral mucosa.

Taste buds are ovoid structures, each containing 50–75 cells, within the stratified epithelium of the tongue and the oral mucosa (Figure 15–6). About half the cells are elongated **gustatory (taste) cells**, which turn over with a 7- to 10-day life span. Other cells present are slender **supportive cells**, immature cells, and basal **stem cells** which divide and give rise to the other two types. The base of each bud rests on the basal lamina and is entered by afferent sensory axons that form synapses on the gustatory cells. At the apical ends of the gustatory cells microvilli project through an opening called the taste pore. Molecules (tastants) dissolved in saliva contact the microvilli through the pore and interact with cell surface taste receptors (Figure 15–6).

Figure 15–6.





Taste buds.

(a): Drawing of a single taste bud shows the gustatory (taste) cells, the supporting cells whose function is not well-understood, and the basal stem cells. Microvilli at the ends of the gustatory cells project through an opening in the epithelium, the taste pore. Afferent sensory axons enter the basal end of taste buds and synapse with the gustatory cells. **(b):** In the stratified squamous epithelium of the tongue surface or oral mucusa, taste buds form as distinct clusters of cells that recognizable histologically even at low magnification. At higher power the taste pore may be visible, as well as the elongated nuclei of gustatory and supporting cells and the fewer, round nuclei of basal stem cells. 140X and 500X. H&E.

Taste buds detect at least five broad categories of tastants: metal ions (salty); hydrogen ions from acids (sour); sugars and related organic compounds (sweet); alkaloids and certain toxins (bitter); and certain amino acids such as glutamate (umami; Jap. *umami*, savory). Salty and sour tastes are produced by ion channels; the other taste categories are mediated by G-protein-coupled receptors. Receptor binding produces depolarization of the gustatory cells, stimulating the sensory nerve fibers which send information to the brain for processing. Conscious perception of tastes in food requires olfactory and other sensations in addition to taste bud activity.

Pharynx

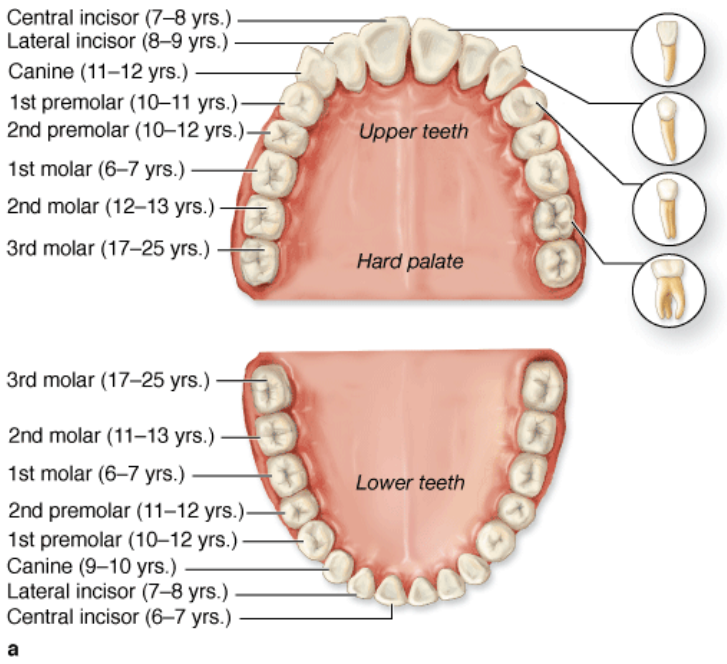
The pharynx, a transitional space between the oral cavity and the respiratory and digestive systems, forms an area of communication between the nasal region and the larynx (Figure 15–1). The pharynx is lined by stratified nonkeratinized squamous epithelium in the region continuous with the esophagus and by ciliated pseudostratified columnar epithelium containing goblet cells in the regions close to the nasal cavity.

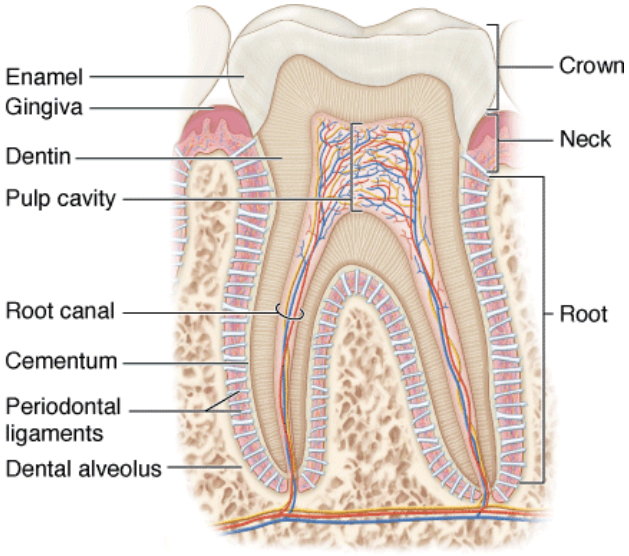
The pharynx contains tonsils (described in Chapter 14) and the mucosa also has many small mucous salivary glands in its lamina propria. The constrictor and longitudinal muscles of the pharynx are located outside this layer.

Teeth

In the adult human there are normally 32 **permanent teeth**, arranged in two bilaterally symmetric arches in the maxillary and mandibular bones (Figure 15–7). Each quadrant has eight teeth: two incisors, one canine, two premolars, and three permanent molars. Twenty of the permanent teeth are preceded by **deciduous** (**baby**) **teeth** which are shed; the others are permanent molars with no deciduous precursors. Each tooth has a **crown** exposed above the gingiva, a constricted **neck** at the gum, and one or more **roots** below the gingiva that hold the teeth in bony sockets called **alveoli,** one for each tooth (Figure 15–7).

Figure 15–7.





Teeth.

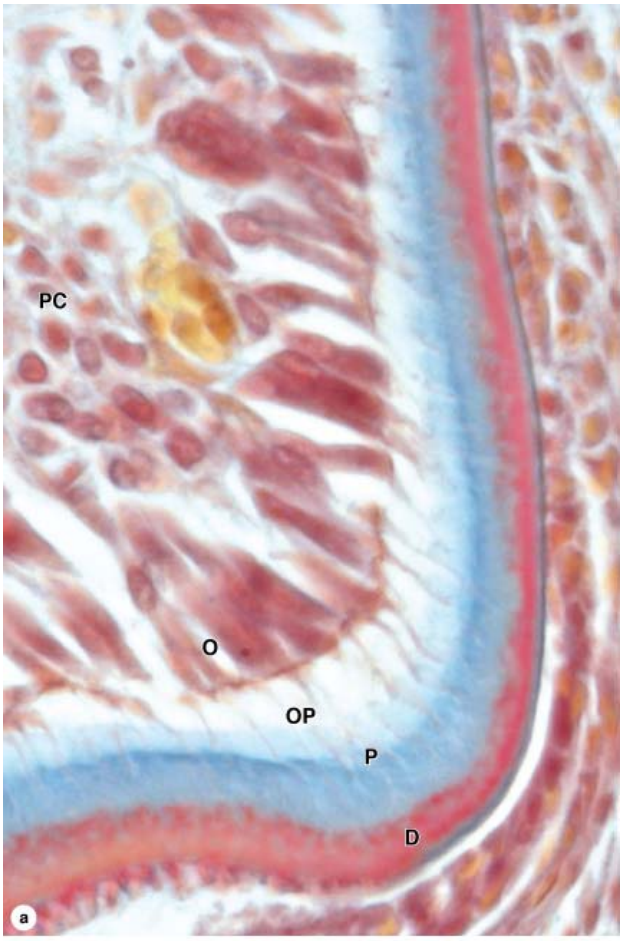
All teeth are similar embryologically and histologically. **(a):** The dentition of the permanent teeth is shown, as well as the approximate age at eruption for each tooth. **(b):** Diagram of a molar's internal structure is similar to that of all teeth, with an enamel-covered **crown**, cementum-covered **roots** anchoring the tooth to alveolar bone of the jaw, and a slightly constricted **neck** where the enamel and cementum coverings meet at the gingiva. A pulp cavity extends into the neck and is filled with well-vascularized, well-innervated mesenchymal connective tissue. Blood vessels and nerves enter the tooth through apical foramina at the root tips.

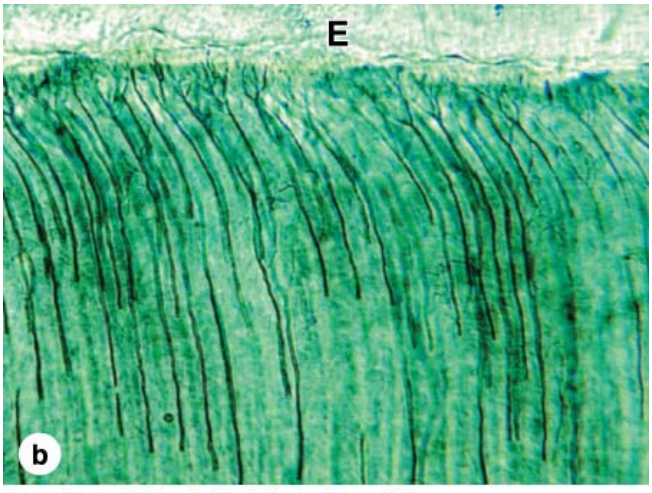
The crown is covered by the extremely hard **enamel** and the roots by a bone-like tissue called **cementum.** These two coverings meet at the neck of the tooth. The bulk of a tooth is composed of another calcified material, **dentin,** which surrounds a soft connective tissue-filled space known as the **pulp cavity** (Figure 15–7). The pulp cavity narrows in the roots as the root canals, which extend to the tip of each root, where an opening (**apical foramen**) permits the entrance and exit of blood vessels, lymphatics, and nerves of the pulp cavity. The **periodontal ligaments** are fibrous connective tissue bundles of collagen fibers inserted into both the cementum and alveolar bone, fixing the tooth firmly in its bony socket (alveolus).

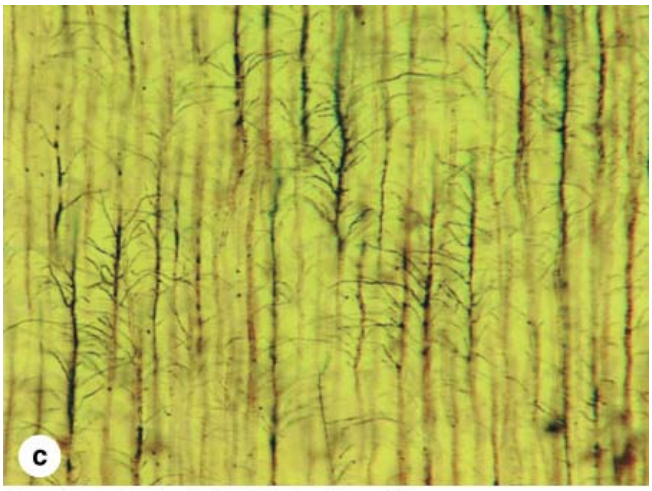
DENTIN

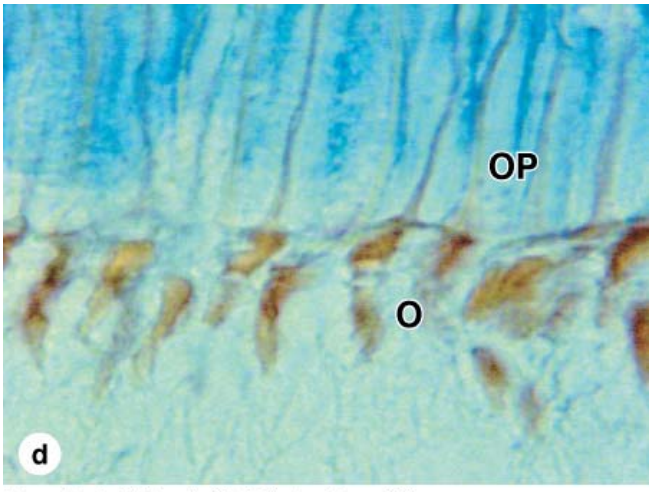
Dentin is a calcified tissue consisting of 70% calcium hydroxyapatite, making it harder than bone. The organic matrix contains type I collagen fibers and glycosaminoglycans secreted by **odontoblasts,** tall polarized cells that line the tooth's internal pulp cavity (Figure 15–8). Mineralization of the **predentin** matrix involves matrix vesicles in a process similar to that in osteoid (Chapter 8). Long, slender apical **odontoblast processes** lie within **dentinal tubules** (Figure 15–9) which penetrate the full thickness of the dentin, gradually becoming longer as the dentin becomes thicker. Along their length the processes extend fine branches into smaller lateral branches of the tubules (Figure 15–8). Odontoblasts remain active in predentin secretion into adult life, gradually reducing the size of the pulp cavity.

Figure 15–8.





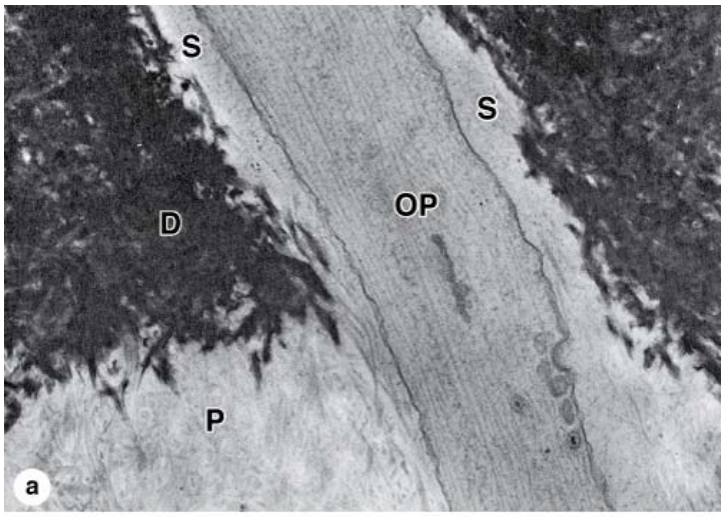


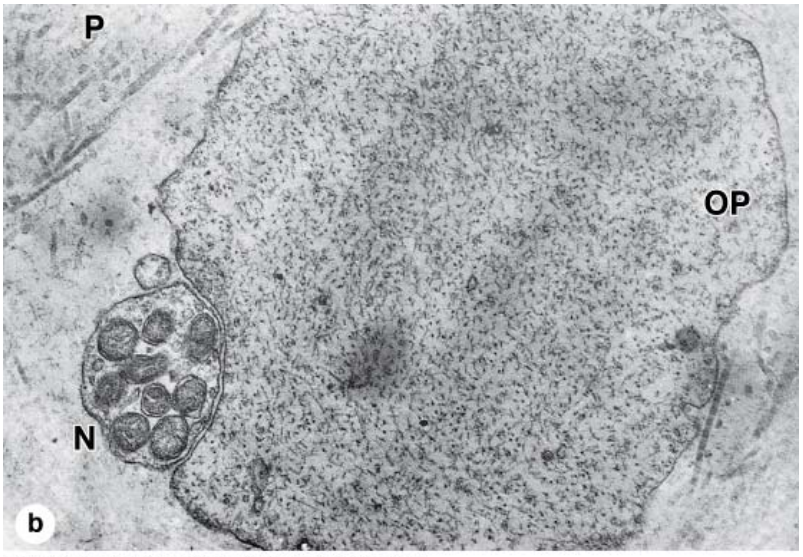


Dentin and odontoblasts.

(a): Odontoblasts (O) are long polarized cells derived from mesenchyme of the developing pulp cavity (PC). Odontoblasts are specialized for collagen and GAG synthesis and are bound together by junctional complexes as a layer, with no basal lamina, so that a collagen-rich matrix called **predentin** (P) is secreted only from their apical ends at the dentinal surface. Within approximately one day of secretion predentin mineralizes to become dentin (D) as hydroxyapatite crystals form in a process similar to that occurring in osteoid of developing bones (Chapter 8). In this process the collagen is masked and calcified matrix becomes much more acidophilic and stains quite differently than that of predentin. When predentin secretion begins an apical extension from each cell, the odontoblast process (OP), forms and is surrounded by new matrix. As the dentin-predentin layer thickens, these processes lengthen. When tooth formation is complete odontoblasts persist and their processes are maintained in canals called dentinal tubules which run through the full thickness of the dentin. X400. Mallory trichrome. (b, c): Odontoblast processes can be silver-stained and shown to branch near the junction of dentin with enamel (E) and along their length closer to their source (c), with the lateral branches occupying smaller canaliculi within dentin. Both X400. Silver. (d): These odontoblast process (OP) connections to the odontoblasts (O), shown with stained nuclei here, are important for the maintenance of dentin in adult teeth. X400. Mallory trichrome. (Figure 15-8b, c and d used, with permission, from M.F. Santos, Department of Histology and Embryology, Institute of Biomedical Sciences, University of São Paulo, Brazil.)

Figure 15–9.





Ultrastructure of dentinal tubule.

(a): TEM shows the calcification of dentin (D) at its border with not-yet- calcified predentin (P). An odontoblast process (OP) with microtubules and a few secretory vesicles occupies much of the space (S) in the dentinal tubule. A process extends from each odontoblast and the tubules continue completely across the dentin layer. X32,000. **(b):** Cross-section of an odontoblast process (OP) near predentin (P) shows its close association with an unmyelinated nerve fiber (N) extending there from fibers in the pulp cavity. These nerves respond to various stimuli, such as cold temperatures, reaching the nerve fibers through the dentinal tubules. X61,000.

Teeth are sensitive to stimuli such as cold, heat, and acidic pH, all of which can be perceived as pain. Pulp is highly innervated and some unmyelinated nerve fibers extend into the dental tubules near the pulp cavity (Figure 15–9). The different stimuli can affect fluid inside dentinal tubules, stimulating these nerve fibers located near odontoblast processes.

MEDICAL APPLICATION

Unlike bone, dentin does not turn over or get remodeled, persisting as a mineralized tissue long after loss of the odontoblasts. It is therefore possible to maintain teeth whose pulp and odontoblasts have been destroyed by infection (canal treatment). In adult teeth, destruction of the covering enamel by erosion from use or dental caries (tooth decay) usually triggers a reaction in odontoblasts that causes them to resume the synthesis of dentin components.

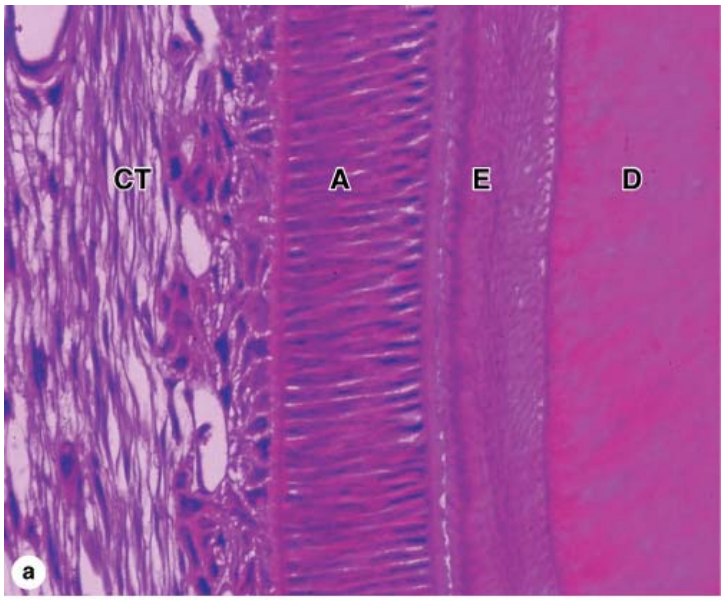
ENAMEL

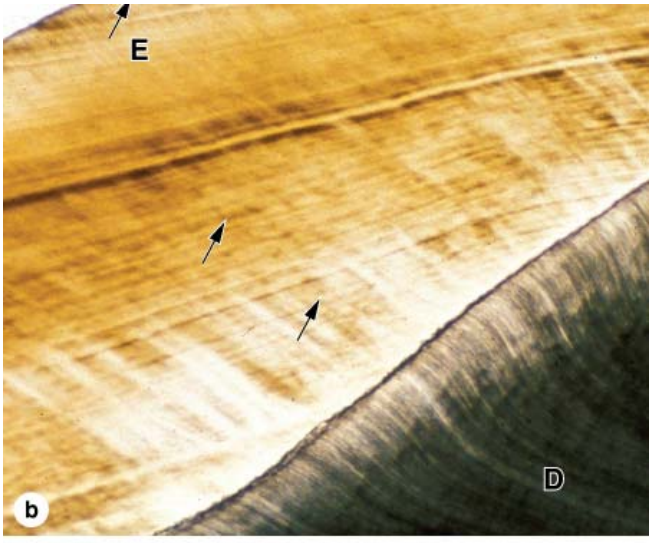
Enamel is the hardest component of the human body, consisting of nearly 98% hydroxyapatite and the rest organic material including at least two unique proteins, **amelogenin** and **enamelin**, but no collagen. Other ions, such as fluoride, can be incorporated or adsorbed by the hydroxyapatite crystals; enamel containing fluorapatite is more resistant to acidic dissolution caused by microorganisms, hence the addition of fluoride to toothpaste and water supplies.

Enamel consists of interlocking rods or columns, **enamel rods** (**prisms**), bound together by other enamel. Each rod extends through the entire thickness of the enamel layer; the precise arrangement of rods in groups is very important for enamel's strength and mechanical properties.

In developing teeth enamel matrix is secreted by a layer of cells called **ameloblasts**, each of which produces one enamel prism (Figure 15–10). An ameloblast is a long, polarized cell with numerous mitochondria, well-developed RER and Golgi apparatus, and an apical extension, the **ameloblast process,** containing numerous secretory granules with proteins for the enamel matrix. After finishing the synthesis of enamel, ameloblasts form a protective epithelium that covers the crown until the eruption of the tooth, a function important in preventing several enamel defects.

Figure 15–10.





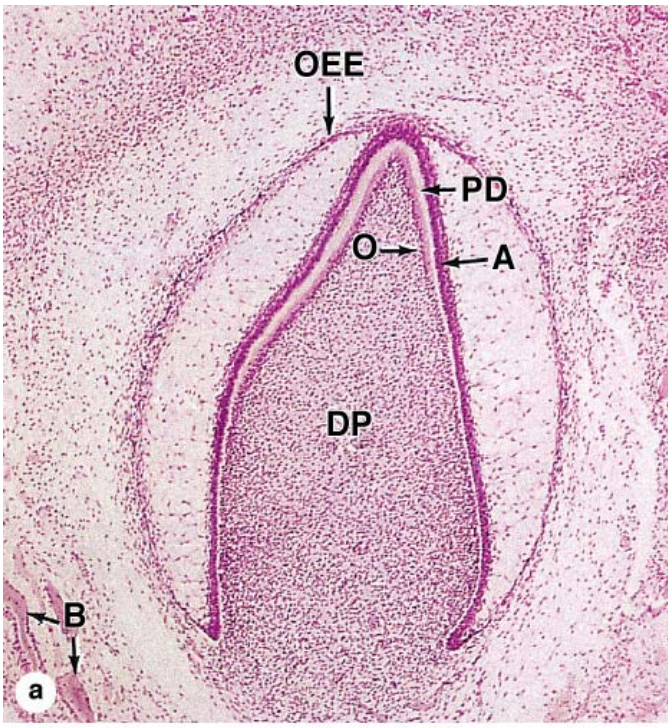
Ameloblasts and enamel.

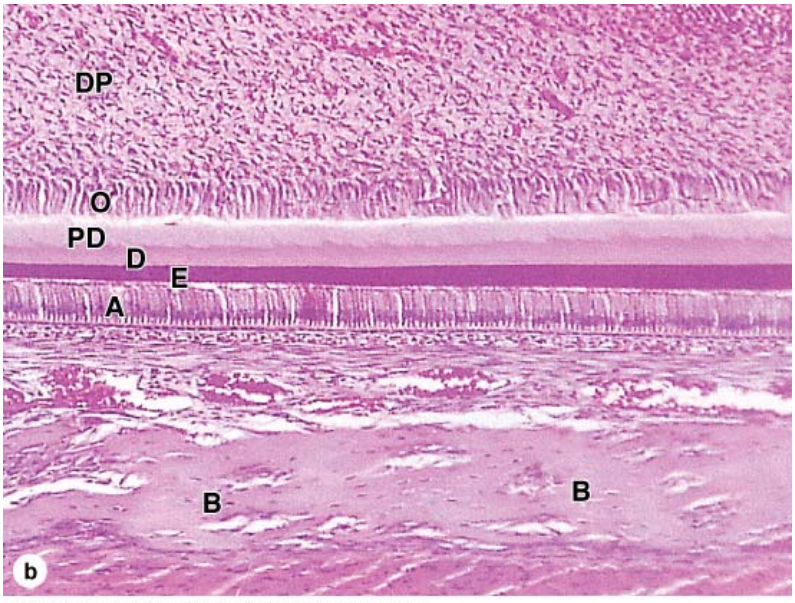
Ameloblasts (A) are tall polarized cells whose apical ends initially contact dentin (D). Ameloblasts are joined to form a cell layer surrounded basally by connective tissue (CT). As odontoblasts secrete predentin, ameloblasts secrete a matrix lacking collagens, but rich in a few glycoproteins which quickly initiate calcium hydroxyapatite formation to make enamel (E), the hardest material in the body. Enamel forms a layer, but consists of enamel rods or prisms, solidly fused together by more enamel. Each enamel rod represents the product of one ameloblast. No cellular processes occur in enamel and the layer of ameloblasts surrounding the developing crown is completely lost during tooth eruption. Teeth that have been decalcified for histological sectioning typically lose their enamel layer completely. X400. H&E.

(b): Micrograph of a thin preparation of a tooth prepared by grinding. Fine tubules can be observed in the dentin (D) and rods aligned the same way can be faintly observed (arrows) in the enamel (E). The more prominent lines that cross enamel diagonally represent incremental growth lines produced as the enamel matrix was secreted cyclically by the ameloblast layer. X400. Unstained.

Enamel is produced by cells of ectodermal origin, whereas most of the other structures of teeth derive from mesodermal and neural crest cells. Together these cells produce a series of structures around the developing oral cavity, the enamel organs, each of which forms one tooth (Figure 15–11).

Figure 15–11.





Tooth formation

Tooth formation begins in the sixth week of human development when ectodermal epithelium lining the oral cavity begins to grow into the underlying mesenchyme of the developing jaws. At a series of sites corresponding to each future tooth, these epithelial cells proliferate extensively and become organized as **enamel organs**, each shaped rather like a wine glass with its stem initially still attached to the oral lining. Ameloblasts form from the innermost layer of cells in the enamel organ. Mesenchymal cells inside the concave portion of the enamel organ include neural crest cells which differentiate as the layer of odontoblasts with their apical ends in contact with the apical ends of the ameloblasts. **(a):** When production of dentin and enamel has begun, the enamel organ appears as shown in this micrograph. The ameloblast layer (A) is separated from the outer enamel epithelium (OEE) by a thick intervening region rich in GAGs but having fewer, widely separated cells. Surrounding the enamel organ is mesenchyme, some parts of which begin to undergo intramembranous bone formation (B) and form the jaws. Inside the cavity of each enamel organ, mesenchymal cells comprise the dental papilla (DP), in which the outermost cells are the layer of odontoblasts (O) facing the ameloblasts. These two cell layers begin to move apart as the odontoblasts begin to produce the layer of predentin (PD). Contact with dentin induces each ameloblast to begin secretion of a rod or prism of enamel matrix. More slowly calcifying interprismatic enamel fuses all the enamel rods into a very strong, solid mass. X20. H&E.

(b): Detail of an enamel organ at a later stage showing the layers of predentin (PD) and dentin (D) and a layer of enamel (E), along with the organized cell layers that produced this material. Odontoblasts (O) are in contact with the very cellular mesenchyme of the dental papilla (DP) which will become the pulp cavity. Ameloblasts (A) are prominent in the now much thinner enamel organ, which is very close to developing bone (B). Details of these cell layers are presented further in Figures 15-8, 15-9 and 15-10. Enamel formation continues until shortly before tooth eruption; formation of dentin continues after eruption until the tooth is fully formed. Odontoblasts persist around the pulp cavity, with processes penetrating the dental layer, producing factors to help maintain dentin. Mesenchymal cells immediately around the enamel organ differentiate into the cells of cementum and other periodontal tissues. X120. H&E.

PULP

Tooth pulp consists of connective tissue resembling mesenchyme. Its main components are the layer of odontoblasts, many fibroblasts, thin collagen fibrils, and ground substance (Figure 15–11). Pulp is a highly innervated and vascularized tissue. Blood vessels and myelinated nerve fibers enter the

apical foramen and divide into numerous branches. Some nerve fibers lose their myelin sheaths and extend into the dentinal tubules. Pulp fibers are sensitive to pain.

GPERIODONTIUM

The periodontium comprises the structures responsible for maintaining the teeth in the maxillary and mandibular bones. It consists of the **cementum, periodontal ligament, alveolar bone,** and **gingiva.**

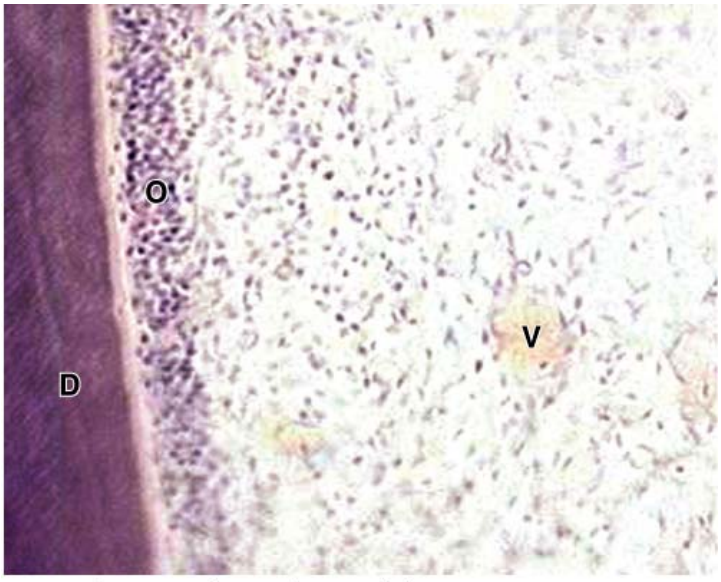
Cementum covers the dentin of the root and is similar in composition to bone, although osteons and blood vessels are absent. It is thicker in the apical region around the root, where there are **cementocytes,** cells resembling osteocytes, in lacunae. Unlike osteocytes, however, cementocytes do not communicate via canaliculi and their nourishment comes from external tissues. Like bone, cementum is labile and reacts to the stresses to which it is subjected by resorbing old tissue or producing new tissue. Continuous production of cementum in the apex compensates for the physiologic wear of the teeth and maintains close contact between the roots of the teeth and their sockets.

MEDICAL APPLICATION

In comparison with bone, the cementum has lower metabolic activity because it is not irrigated by blood vessels. This feature allows the movement of teeth within alveolar bone by orthodontic appliances without significant root resorption.

The **periodontal ligament** is connective tissue 150 to 350 µm thick with collagen fiber bundles connecting the cementum and the alveolar bone of the tooth socket (Figure 15–12). It permits limited movement of the tooth within the socket and the fibers are organized to support the pressures exerted during mastication. This avoids transmission of pressure directly to the bone which would cause localized bone resorption. Unlike typical ligaments, it is highly cellular and has a rich supply of blood vessels and nerves, giving the periodontal ligament supportive, protective, sensory, and nutritive functions. Collagen of the periodontal ligament has an unusually high turnover rate (as demonstrated by autoradiography) and a high content of soluble collagens, with the space between its fibers filled with glycosaminoglycans (GAGs).

Figure 15–12.



Dental Pulp.

The periphery of the dental pulp contains the organized odontoblasts (O) contacting the surrounding dentin (D). Centrally the pulp consists of delicate, highly cellular connective tissue resembling undifferentiated mesenchyme but with many thin-walled venules (V) and capillaries. Pulp has reticulin fibers and other fine collagen fibers, with much ground substance. Nerves fibers are also present. The blood and nerve supplies enter the pulp cavity via the apical foramen at the apex of the roots. X150. H&E.

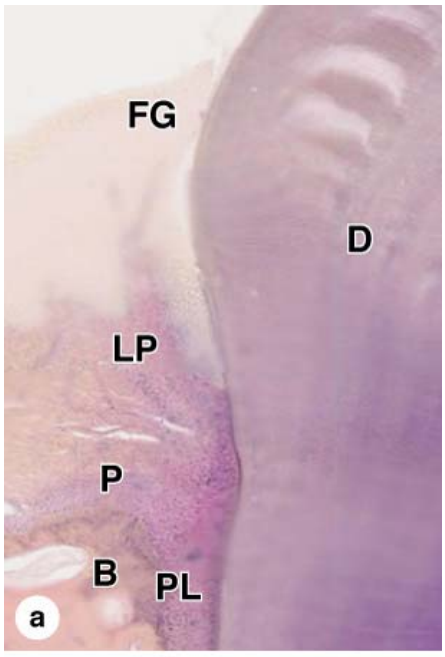
MEDICAL APPLICATION

The high rate of collagen renewal in the periodontal ligament allows processes affecting protein or collagen synthesis, eg, protein or vitamin C deficiency (**scurvy**), to cause atrophy of this ligament. As a consequence, teeth become loose in their sockets; in extreme cases they fall out.

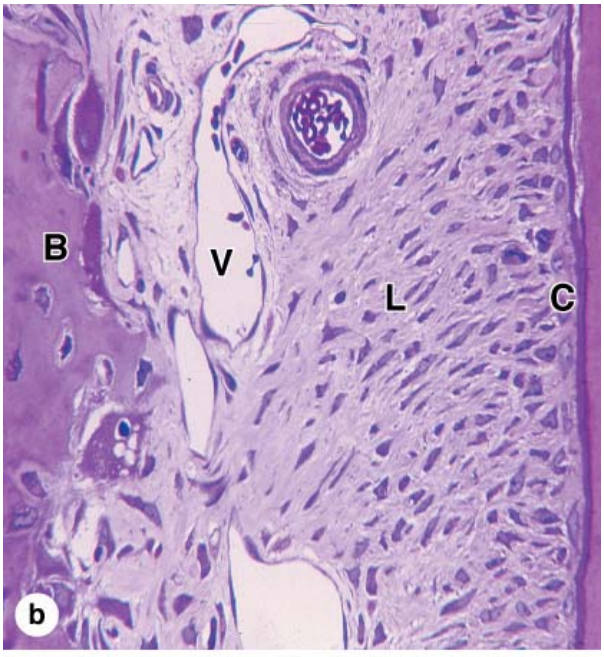
The **alveolar bone** is in immediate contact with the periodontal ligament, which serves as its periosteum. It is primary (immature) bone, with the collagen fibers not arranged in the typical lamellar pattern of adult bone. Many of the collagen fiber bundles of the periodontal ligament penetrate this bone and bind it to the cementum (Figure 15–12). The bone closest to the roots of the teeth forms the socket. Vessels run through the alveolar bone and penetrate the periodontal ligament along the root, with some vessels and nerves entering the pulp at the apical foramen of each root.

The **gingiva** is a mucous membrane firmly bound to the periosteum of the maxillary and mandibular bones (Figure 15–13). It is composed of stratified squamous epithelium and lamina propria with numerous connective tissue papillae. A specialized part of this epithelium, named **junctional epithelium,** is bound to the tooth enamel by means of a cuticle resembling a thick basal lamina. The epithelial cells are attached to this cuticle by numerous hemidesmosomes. Between the enamel and the epithelium is the **gingival sulcus,** a groove up to 3 mm deep surrounding the neck (Figure 15–13a).

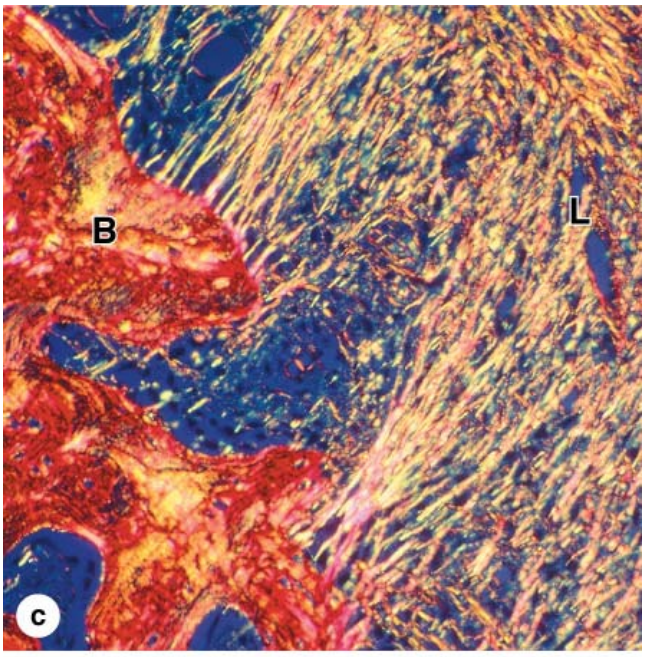
Figure 15–13.



Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com



Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com



Periodontium.

The periodontium of each tooth consists of the **cementum, periodontal ligament, alveolar bone,** and **gingiva**. **(a):** Micrograph of decalcified tooth showing the gingiva. The free gingiva (FG) is against the dentin (D), with little of the gingival sulcus apparent. Gingiva has many layers of stratified epithelial cells covering the connective tissue of the lamina propria (LP). The connective tissue is continuous with that of the periosteum (P) covering the alveolar bone (B) and with the periodontal ligament (PL). X10. H&E.

(b): Micrograph shows the periodontal ligament (L) with its many blood vessels (V) and insertions into the alveolar bone (B). This ligament serves as the periosteum of the alveolar in tooth sockets and is also continuous with developing layers of cementum (C) that covers the dentin. Cementum forms a thin layer of bone-like material secreted by large, elongated cells called cementoblasts. X100. H&E. **(c):** Micrograph shows the continuity of collagen fibers in alveolar bone (B) with the bundles in the periodontal ligament (L). X200. Picrosirius in polarized light.

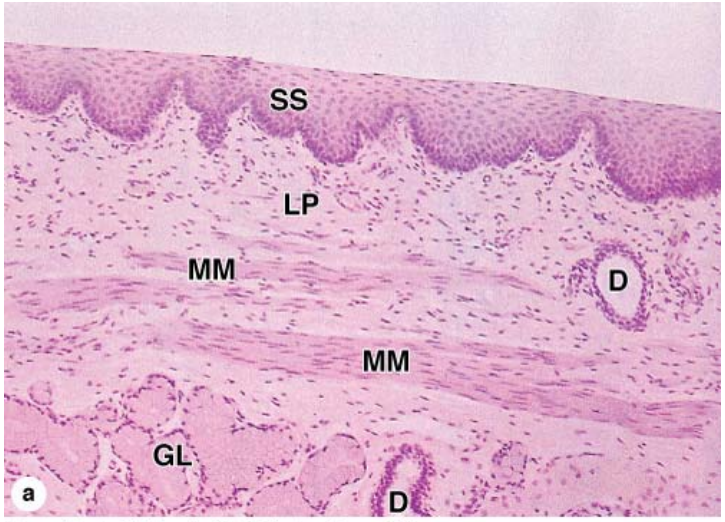
MEDICAL APPLICATION

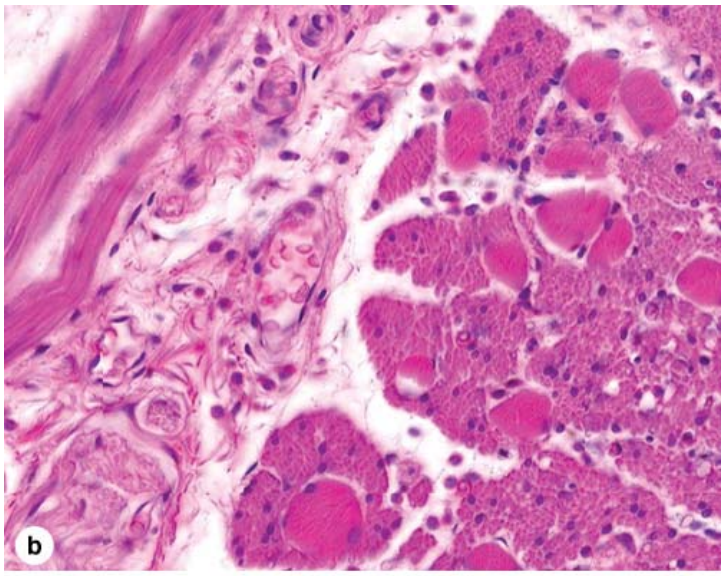
The depth of the gingival sulcus, measured during clinical dental examinations, is an important indicator of potential periodontal disease.

ESOPHAGUS

The part of the gastrointestinal tract called the **esophagus** is a muscular tube whose function is to transport food from the mouth to the stomach. It is lined by nonkeratinized stratified squamous epithelium with stem cells scattered throughout the basal layer (Figure 15–14). In general, the esophagus has the same major layers as the rest of the digestive tract. In the submucosa are groups of small mucus-secreting glands, the **esophageal glands,** secretions of which facilitate the transport of foodstuffs and protect the mucosa. In the lamina propria of the region near the stomach are groups of glands, the **esophageal cardiac glands**, which also secrete mucus.

Figure 15–14.





Esophagus.

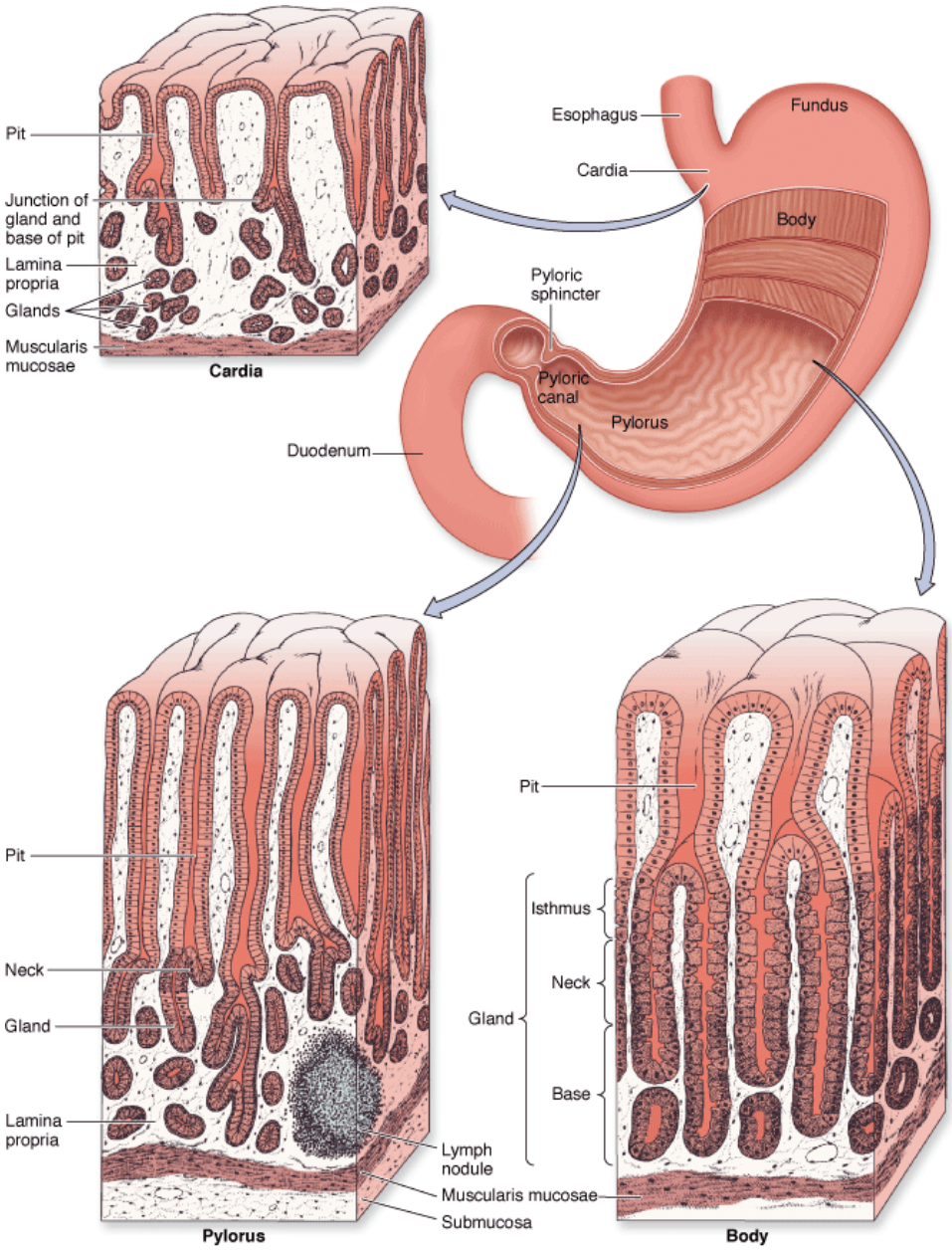
(a): Longitudinal section of esophagus shows mucosa consisting of nonkeratinized stratified squamous epithelium (SS), lamina propria (LP), and smooth muscles of the muscularis mucosae (MM). Beneath the mucosa is the submucosa containing esophageal mucous glands (GL) which empty via ducts (D) onto the luminal surface. X40. H&E. **(b):** Transverse section showing the muscularis halfway along the esophagus reveals a combination of skeletal muscle (right) and smooth muscle fibers (left) in the outer layer, which are cut both longitudinally and transversely here. This transition from muscles under voluntary control to the type controlled autonomically is important in the swallowing mechanism. X200. H&E.

Swallowing begins with controllable motion, but finishes with involuntary peristalsis. In the proximal third of the esophagus the muscularis is exclusively skeletal muscle like that of the tongue. The middle third contains a combination of skeletal and smooth muscle fibers (Figure 15–14) and in the distal third the muscularis contains only smooth muscle. Also, only the most distal portion of the esophagus, in the peritoneal cavity, is covered by serosa. The rest is enclosed by a layer of loose connective tissue, the adventitia, which blends into the surrounding tissue.

STOMACH

The stomach, like the small intestine, is a mixed exocrine-endocrine organ that digests food and secretes hormones. It is a dilated segment of the digestive tract whose main functions are to continue the digestion of carbohydrates initiated in the mouth, add an acidic fluid to the ingested food, transform it by muscular activity into a viscous mass (**chyme**), and promote the initial digestion of proteins with the enzyme **pepsin.** It also produces a gastric lipase that digests triglycerides . Gross inspection reveals four regions: **cardia, fundus, body,** and **pylorus** (Figure 15–15). The fundus and body are identical in microscopic structure so that only three histologically distinct regions are recognized. The mucosa and submucosa of the empty stomach have longitudinally directed folds known as **rugae**, which flatten when the stomach is filled with food. The wall in all regions of the stomach is made up of all four major layers (Figure 15–16).

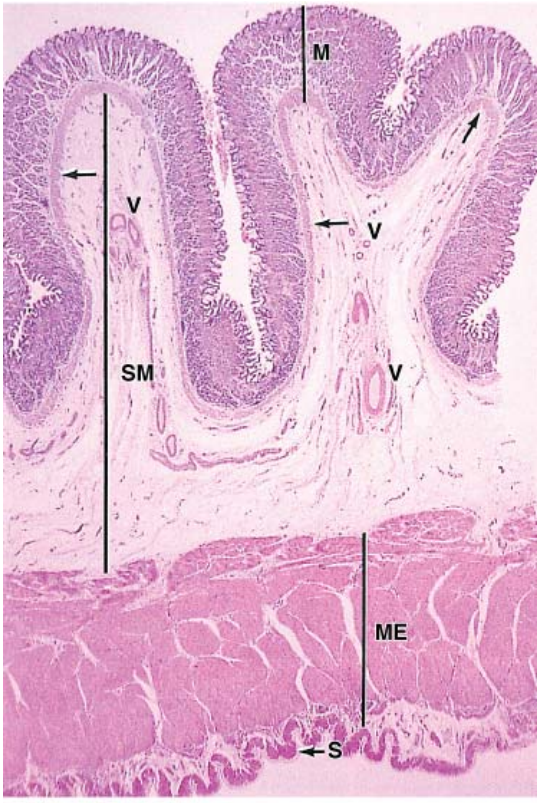
Figure 15–15.



Regions of the stomach.

The stomach is a muscular dilation of the digestive tract where mechanical and chemical digestion occurs. The muscularis consists of three layers for thorough mixing of the stomach contents as chyme: an outer longitudinal layer, a middle circular layer, and an inner oblique layer. The stomach mucosa shows distinct histological differences in the cardia, the fundus/body, and the pylorus. Cells that secrete HCl and pepsin are restricted mainly to the body and fundus regions. Glands of the cardia and pylorus produce primarily mucus.

Figure 15–16.



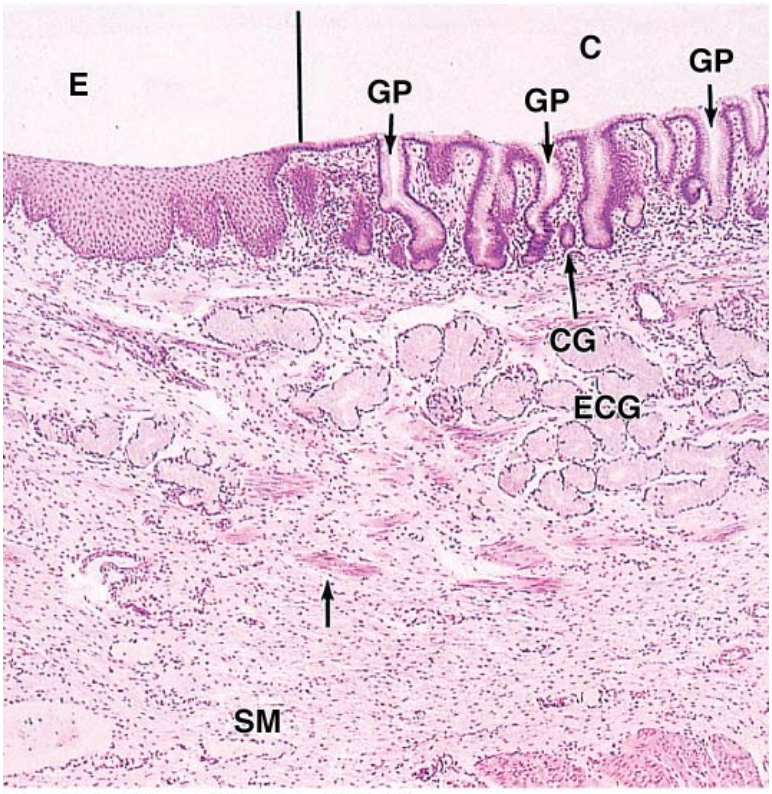
Wall of the stomach with rugae.

Low magnification micrograph of the stomach wall at the fundus shows the relative thickness of the four major layers: the mucosa (M), the submucosa (SM), the muscularis externa (ME), and the serosa (S). Two rugae (folds) cut transversely and consisting of mucosa and submucosa are included. The mucosa is packed with branched tubular glands penetrating the full thickness of the lamina propria so that this sublayer cannot be distinguished at this magnification. The muscularis mucosae (arrows), immediately beneath the basal ends of the gastric glands, is shown. The submucosa is largely loose connective tissue, with blood vessels (V) and lymphatics. X12. H&E.

Mucosa

Changing abruptly at the esophago-gastric junction, the mucosa of the stomach consists of a simple columnar **surface epithelium** that invaginates into the lamina propria, forming **gastric pits** (Figures 15–17 and 15–18). Emptying into the gastric pits are branched, tubular glands characteristic of the stomach region (cardiac, gastric, and pyloric). Stem cells for the entire epithelial lining of the stomach are located in the upper regions of these glands near the gastric pits. The vascularized **lamina propria** that surrounds and supports these pits and glands contains smooth muscle fibers and lymphoid cells. Separating the mucosa from the underlying submucosa is a layer of smooth muscle, the **muscularis mucosae** (Figure 15–16).

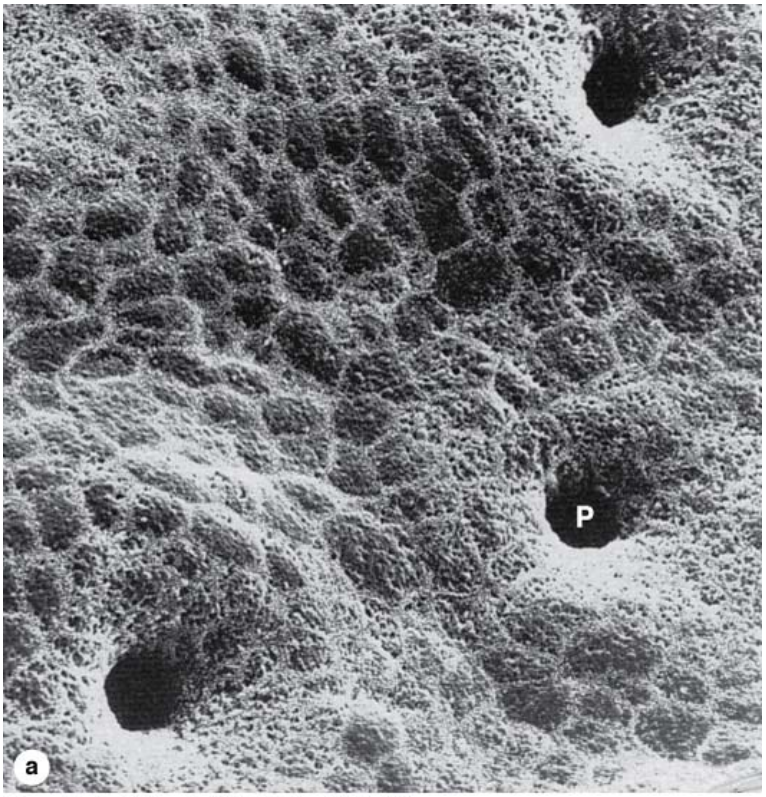
Figure 15–17.

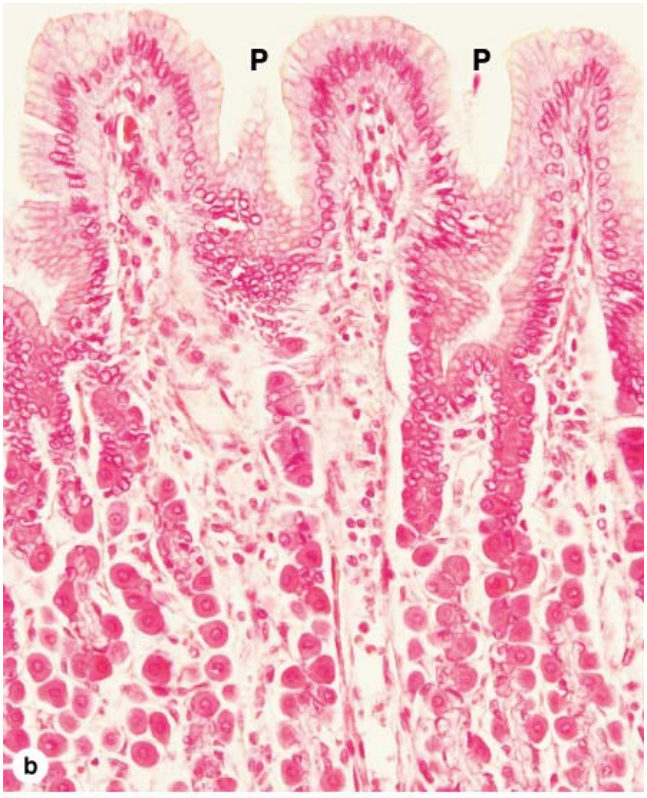


Esophagogastric junction.

At the junction of the esophagus (E) and the cardiac region of the stomach (C) there is an abrupt change in the mucosa from stratified squamous epithelium to simple columnar epithelium invaginating as gastric pits (GP). The mucosa contains many mucus-secreting esophageal cardiac glands (ECG), whose function is supplemented by mucous cardiac glands (CG) opening into the superficial gastric pits. Strands of muscularis mucosae (arrow) separate the mucosa and submucosa (SM). X60. H&E.

Figure 15–18.





Gastric pits and glands.

(a): SEM of the stomach lining cleared of its mucus layer reveals closely placed gastric pits (P) surrounded by polygonal apical ends of surface mucous cells. X600. **(b):** Micrograph of the same lining shows that these surface mucous cells are part of a simple columnar epithelium continuous with the lining of the pits (P). Each pit extends into the lamina propria and then branches into several tubular glands. These glands branch further, coil slightly, and fill most of the volume of the mucosa. Around the glands, which contain other cells besides columnar cells, a small amount of connective tissue comprising the lamina propria is also seen. X200. H&E.

When the luminal surface of the stomach is viewed under low magnification, numerous small circular or ovoid invaginations of the epithelial lining are observed. These are the openings of the gastric pits (Figures 15–17 and 15–18). The epithelium covering the surface and lining the pits is a simple columnar epithelium, the cells of which produce a protective mucus layer. Glycoproteins secreted by the epithelial cells are hydrated and mix with lipids and bicarbonate ions also released from the epithelium to form a thick, hydrophobic layer of gel with a pH gradient from almost 1 at the luminal surface to 7 at the epithelial cells. The mucus firmly adherent to the epithelial surface is very effective in protection, while the superficial luminal mucus layer is more soluble, partially digested by pepsin and mixed with the luminal contents. Hydrochloric acid, pepsin, lipases, and bile in the stomach lumen must all be considered as potential endogenous aggressors to the epithelial lining. Surface epithelial cells also form an important line of defense due to their mucus production, their tight intercellular junctions, and ion transporters to maintain intracellular pH and bicarbonate production. A third line of defense is the underlying circulatory bed, which provides bicarbonate ions, nutrients, and oxygen to the mucosal cells, while removing toxic metabolic products. The rich vasculature also favors the rapid healing of superficial wounds to the mucosa.

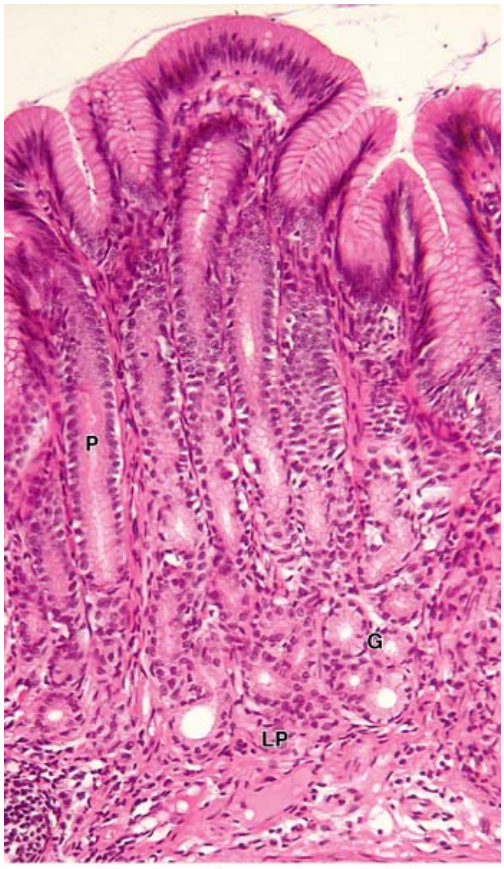
MEDICAL APPLICATION

Stress and other psychosomatic factors; ingested substances such as aspirin, nonsteroidal anti-inflammatory drugs or ethanol; the hyperosmolality of meals; and some microorganisms (eg, Helicobacter pylori) can disrupt this epithelial layer and lead to **ulceration**. The initial ulceration may heal, or it may be further aggravated by the local aggressive agents, leading to additional gastric and duodenal ulcers. Processes that enable the gastric mucosa to rapidly repair superficial damage incurred by several factors play a very important role in the defense mechanism, as does an adequate blood flow that supports gastric physiologic activity. Any imbalance between aggression and protection may lead to pathologic alterations. As an example, aspirin and ethanol irritate the mucosa partly by reducing mucosal blood flow. Several anti-inflammatory drugs inhibit the production of prostaglandins of the E type, which are very important substances for the alkalinization of the mucus layer and, consequently, important for protection.

REGIONAL DIFFERENCES IN THE STOMACH MUCOSA

The **cardia** is a narrow circular region, only 1.5–3 cm in width, at the transition between the esophagus and the stomach (Figure 15–15). The **pylorus** is the funnel-shaped region opening into the small intestine. The mucosa of these two stomach regions contains tubular glands, usually branched, with coiled secretory portions called **cardial glands** and **pyloric glands** (Figure 15–19). The pits leading to these glands are longer in the pylorus. In both regions the glands secrete abundant **mucus**, as well as **lysozyme**, an enzyme that attacks bacterial walls.

Figure 15–19.



Pyloric glands.

The pyloric region of the stomach has deep gastric pits (P) leading to short, coiled pyloric glands (G) in the lamina propria. Cardial glands are rather similar histologically and functionally. Cells of these glands secrete mucus and lysozyme primarily, with a few G cells also present. The glands and pits are surrounded by cells of the lamina propria (LP), connective tissue also containing lymphatics and MALT. Immediately beneath the glands is the smooth muscle layer of the muscularis mucosae. X140. H&E.

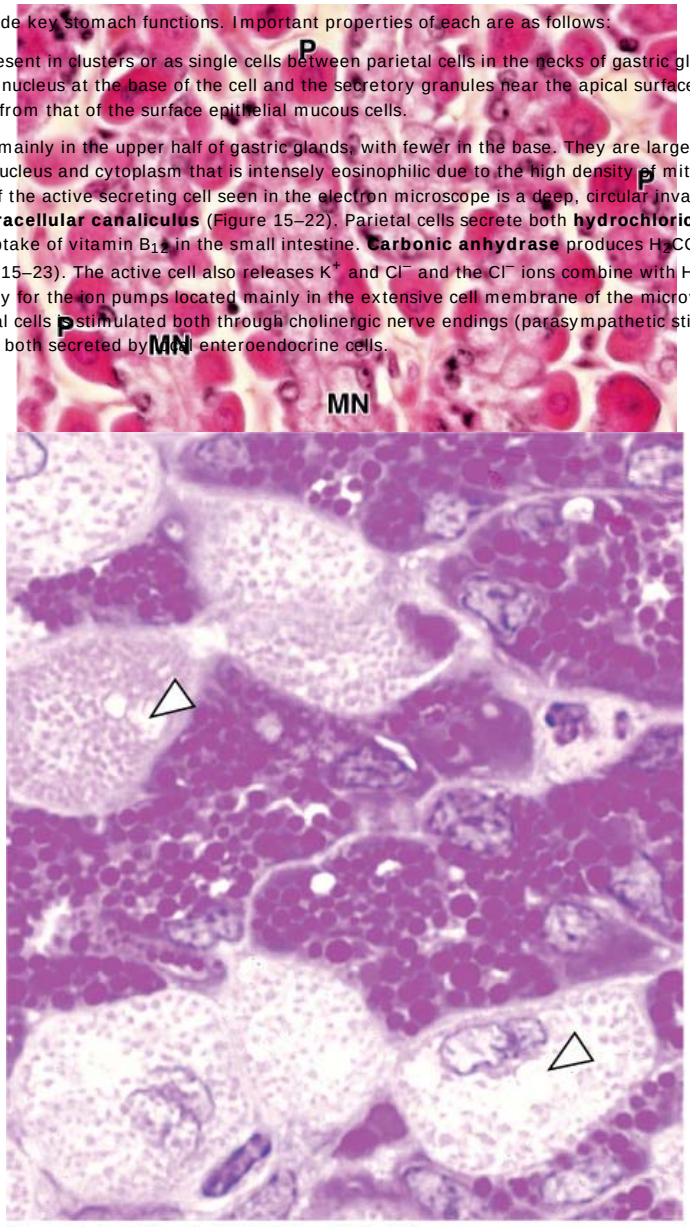
In the **fundus** and **body**, the mucosa's lamina propria is filled with branched, tubular **gastricglands,** three to seven of which open into the bottom of each gastric pit. Each gastric gland has an isthmus, a neck, and a base; the distribution of epithelial cells in the glands is not uniform (Figures 15–15 and 15–20). The **isthmus**, near the gastric pit, contains differentiating mucous cells that migrate and replace surface mucous cells, a few undifferentiated stem cells, and a few parietal (oxyntic) cells; the **neck** of the glands consists of stem cells, mucous neck cells (different from the isthmus mucous cells), and parietal cells (Figure 15–20); the **base** of the glands contains parietal cells and chief (zymogenic) cells. Various enteroendocrine cells are dispersed in the neck and the base of the glands.

Figure 15–20.

These cells of the gastric glands provide key stomach functions. Important properties of each are as follows:

- **Mucous neck cells** are present in clusters or as single cells between parietal cells in the necks of gastric glands (Figure 15–20a). They are irregular in shape, with the nucleus at the base of the cell and the secretory granules near the apical surface. Their mucus secretion is less alkaline and quite different from that of the surface epithelial mucous cells.
- **Parietal cells** are present mainly in the upper half of gastric glands, with fewer in the base. They are large rounded or pyramidal cells, each with one central spherical nucleus and cytoplasm that is intensely eosinophilic due to the high density of mitochondria (Figures 15–20 and 15-21). A striking feature of the active secreting cell seen in the electron microscope is a deep, circular invagination of the apical plasma membrane, forming an **intracellular canaliculus** (Figure 15–22). Parietal cells secrete both **hydrochloric acid (HCl)** and **intrinsic factor**, a glycoprotein required for uptake of vitamin B_{12} in the small intestine. **Carbonic anhydrase** produces H_2CO_3 which dissociates in the cytoplasm into H^+ and HCO_3^+ (Figure 15–23). The active cell also releases K^+ and Cl^- and the Cl^- ions combine with H^+ to form HCl. The abundant mitochondria provide energy for the ion pumps located mainly in the extensive cell membrane of the microvilli projecting into the canaliculi. Secretory activity of parietal cells is stimulated both through cholinergic nerve endings (parasympathetic stimulation) and by histamine and a polypeptide called **gastrin,** both secreted by local enteroendocrine cells.

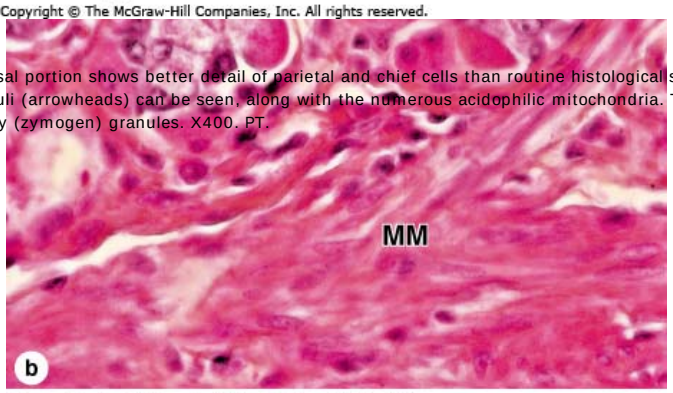
Figure 15–21.



Parietal cells and chief cells.

A plastic section of a gastric gland's basal portion shows better detail of parietal and chief cells than routine histological sections often allow. The large parietal cells' characteristic intracellular canaliculi (arrowheads) can be seen, along with the numerous acidophilic mitochondria. The smaller chief cells have cytoplasm containing numerous large red secretory (zymogen) granules. X400. PT.

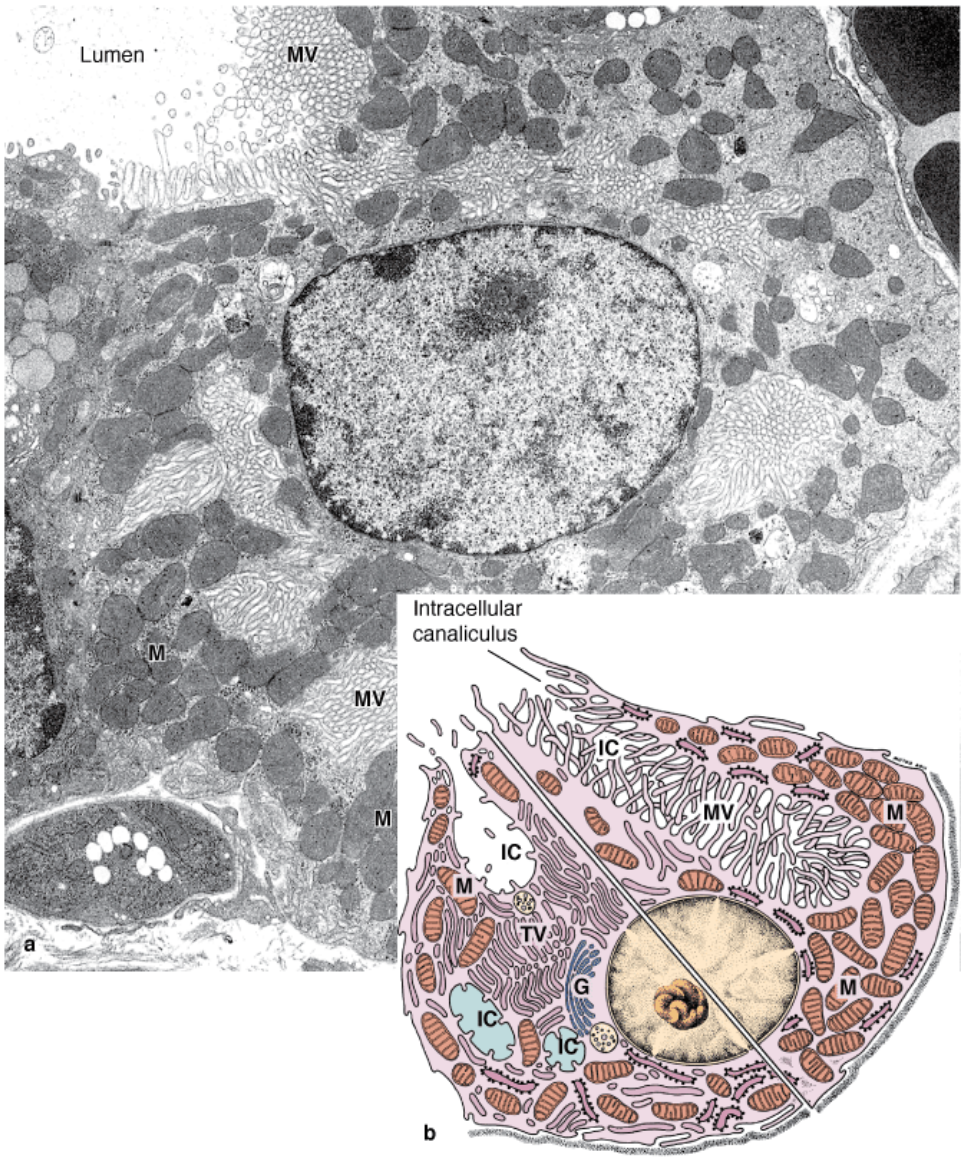
Figure 15–22.



Gastric glands.

Throughout the fundus and body regions of the stomach the gastric pits lead to glands with various cell types. **(a):** In the neck of the glands are mucous neck cells (MN), scattered or present as clusters of irregular, low columnar cells with basophilic, granular cytoplasm and basal nuclei. These cells produce mucus with a higher content of glycoproteins than that made by surface mucous cells. Among the neck mucous cells are stem cells that give rise to all epithelial cells of the glands. In the upper half of the glands are also numerous distinctive parietal cells (P), large rounded cells often bulging from the tubules, with large central nuclei surrounded by intensely eosinophilic cytoplasm with unusual ultrastructure. These cells produce HCl and the numerous mitochondria required for this process cause the eosinophilia. Around these tubular glands are various cells and microvasculature in connective tissue.

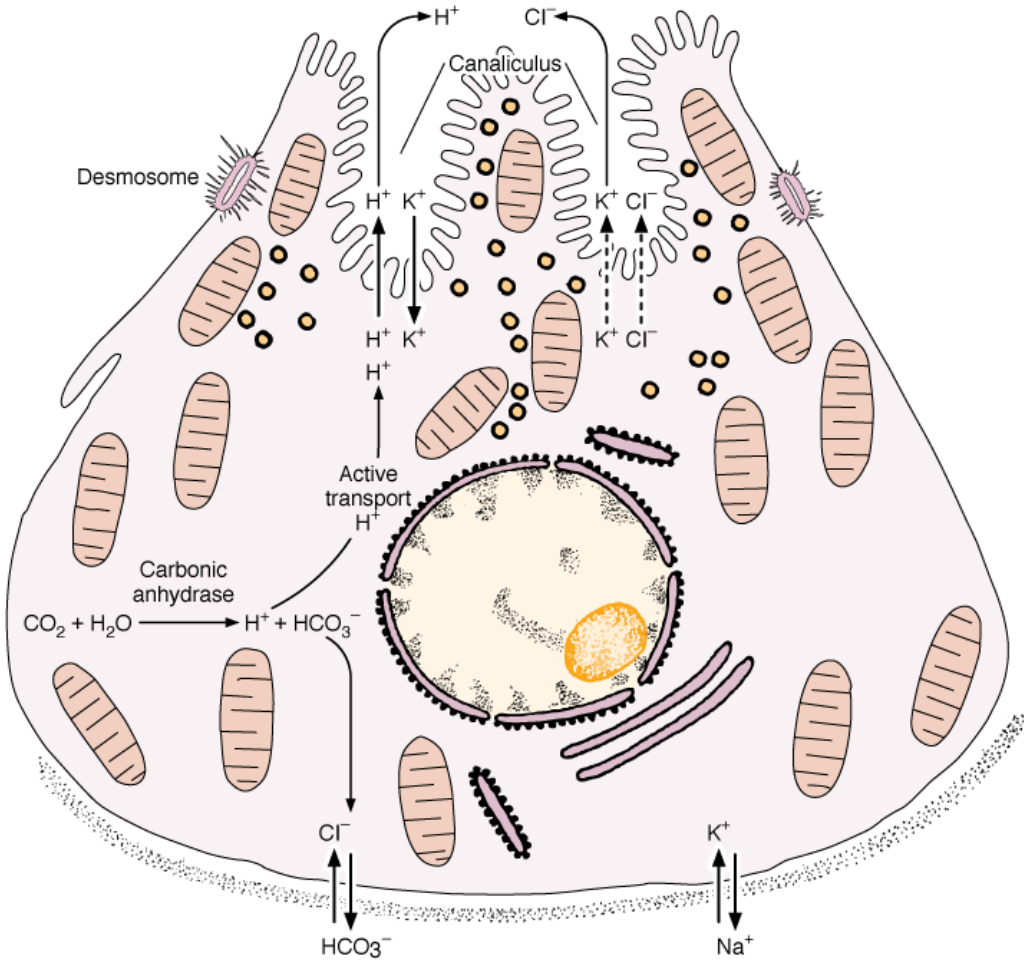
(b): Near the muscularis mucosae (MM), the bases of these glands contain fewer parietal cells, but another cell type, chief cells (C), is abundant here. Chief cells are also known as peptic or zymogenic cells. They are seen as clusters of cells with condensed, basal nuclei and basophilic cytoplasm. From their apical ends chief cells secrete pepsinogen, the zymogen precursor for pepsin, a major protease. Zymogen granules are often removed or stain poorly in routine preparations. Both X200. H&E.



Ultrastructure of parietal cells.

(a): A TEM of an active parietal cell shows abundant microvilli (MV) protruding into the intracellular canaliculi, near the lumen and deep in the cell. The remaining cytoplasm is filled with mitochondria (M). X10,200. **(b):** Composite diagram of a parietal cell, showing the ultrastructural differences between a resting cell (left) and an active cell (right). In the resting cell, a number of tubulovesicular structures can be seen in the apical region just below the plasmalemma (left), but the cell has few microvilli. When stimulated to produce hydrochloric acid (right), these vesicles fuse with the cell membrane to form the canaliculus and microvilli, thus providing a generous increase in the surface of the cell membrane for diffusion and ion pumps. (Figure 15-22a, with permission, from Dr. Susumu Ito, Department of Cell Biology, Harvard Medical School.)

Figure 15–23.



Synthesis of HCl by parietal cells.

Diagram showing the main steps in the synthesis of hydrochloric acid. Active transport by ATPase is indicated by arrows and diffusion is indicated by dotted arrows. Under the action of carbonic anhydrase, carbonic acid is produced from CO_2. Carbonic acid dissociates into a bicarbonate ion and a proton (H^+), which is pumped into the stomach lumen in exchange for K^+. A high concentration of intracellular K^+ is maintained by the Na^+, K^+ ATPase, while HCO_3^- is exchanged for Cl^- by an antiport. The tubulovesicles of the cell apex are seen to be related to hydrochloric acid secretion, because their number decreases after parietal cell stimulation as microvilli increase. Most of the bicarbonate ion returns to the blood and is responsible for a measurable increase in blood pH during digestion, but some is taken up by surface mucous cells and used to raise the pH of mucus.

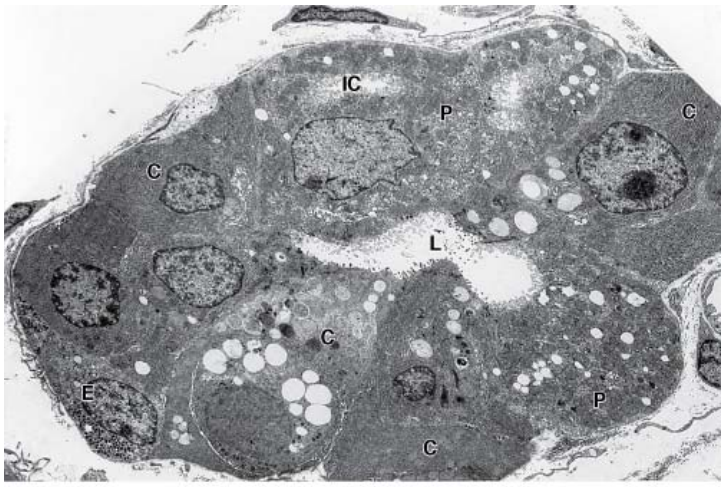
MEDICAL APPLICATION

In cases of **atrophic gastritis**, both parietal and chief cells are much less numerous, and the gastric juice has little or no acid or pepsin activity. In humans, parietal cells are the site of production of intrinsic factor, a glycoprotein that binds avidly to vitamin B12 . In other species, however, the intrinsic factor may be produced by the chief cells.

The complex of vitamin B12 with intrinsic factor is absorbed by pinocytosis into the cells in the ileum; this explains why a lack of intrinsic factor can lead to vitamin B_{12} deficiency. This condition results in a disorder of the erythrocyte-forming mechanism known as **pernicious anemia**, usually caused by atrophic gastritis. In a certain percentage of cases, pernicious anemia seems to be an autoimmune disease, because antibodies against parietal cell proteins are often detected in the blood of patients with the disease.

- **Chief (zymogenic) cells** predominate in the lower region of the tubular glands (Figure 15–24) and have all the characteristics of protein-synthesizing and -exporting cells. The cytoplasmic granules contain the inactive enzyme **pepsinogen.** This precursor is rapidly converted into the highly active proteolytic enzyme **pepsin** after being released into the acid environment of the stomach. Pepsins are aspartate endoproteinases of relatively broad specificity, active at pH <5. In humans chief cells also produce the enzyme lipase and the hormone leptin.
- **Enteroendocrine cells** are an epithelial cell type in the mucosa throughout the digestive tract, but are difficult to detect by routine H&E staining. Different enteroendocrine cells secrete a variety of hormones, almost all short polypeptides (Table 15–1). They can be distinguished by TEM but are most easily identified by immunohistochemistry. In the fundus **enterochromaffin cells (EC cells)** are found on the basal lamina of gastric glands (Figure 15–24) and secrete principally **serotonin (5-hydroxytryptamine)**. In the pylorus and lower body of the stomach other enteroendocrine cells are located in contact with the glandular lumens, including **Gcells** which produce the polypeptide **gastrin**. Gastrin stimulates the secretion of acid by parietal cells and has a trophic effect on gastric mucosa.
- **Stem cells** are few in number and found in the neck region of the glands. They are low columnar cells with basal nuclei and divide asymmetrically (Figure 3–20). Some of the daughter cells move upward to replace the pit and surface mucous cells, which have a turnover time of 4–7 days. Other daughter cells migrate more deeply into the glands and differentiate into mucous neck cells and parietal, chief, and enteroendocrine cells. These cells are replaced much more slowly than are surface mucous cells.

Figure 15–24.



Ultrastructure of parietal, chief, and enteroendocrine cells.

TEM of a transversely sectioned gastric gland shows the ultrastructure of three major cell types. Parietal cells (P) contain abundant mitochondria and intracellular canaliculi (IC). Most of the cells are chief cells (C), which have extensive rough ER and apical secretory granules near the lumen (L). An enteroendocrine cell (E) shows dense basal secretory granules. This example is an enterochromaffin cell (EC cell) secreting serotonin. It is a closed type enteroendocrine cell, ie, it has no contact with the gland's lumen, and secretes product in an endocrine/paracrine manner. X5300.

Table 15–1. Principal enteroendocrine cells in the gastrointestinal tract.

Cell Type and Location	Hormone Produced	Major Action
X/A-like—stomach	Ghrelin	Increase sense of hunger
G—pylorus	Gastrin	Stimulation of gastric acid secretion
S—small intestine	Secretin	Pancreatic and biliary bicarbonate and water secretion
K—small intestine	Gastric inhibitory polypeptide	Inhibition of gastric acid secretion
L—small intestine	Glucagon-like peptide 1 (GLP-1)	Decrease sense of hunger
I—small intestine	Cholecystokinin (CCK)	Pancreatic enzyme secretion, gallbladder contraction
D—pylorus, duodenum	Somatostatin	Local inhibition of other endocrine cells
Mo—small intestine	Motilin	Increased gut motility
EC—digestive tract	Serotonin, substance P	Increased gut motility
D_1—digestive tract	Vasoactive intestinal polypeptide (VIP)	Ion and water gut motility secretion, increased

MEDICAL APPLICATION

Tumors called **carcinoids**, which arise from the EC cells, are responsible for the clinical symptoms caused by overproduction of serotonin. Serotonin increases gut motility, but high levels of this hormone/neurotransmitter have been related to mucosal vasoconstriction and damage.

Other Layers of the Stomach

The **submucosa** is composed of connective tissue containing blood and lymph vessels; it is infiltrated by lymphoid cells, macrophages, and mast cells. The **muscularis** is composed of smooth muscle fibers oriented in three main directions. The external layer is longitudinal, the middle layer is circular, and the internal layer is oblique. Rhythmic contractions of the muscularis serve to mix ingested food and chyme with the secretions from the gastric mucosa. At the pylorus, the middle layer is greatly thickened to form the **pyloric sphincter.** The stomach is covered by a thin **serosa.**

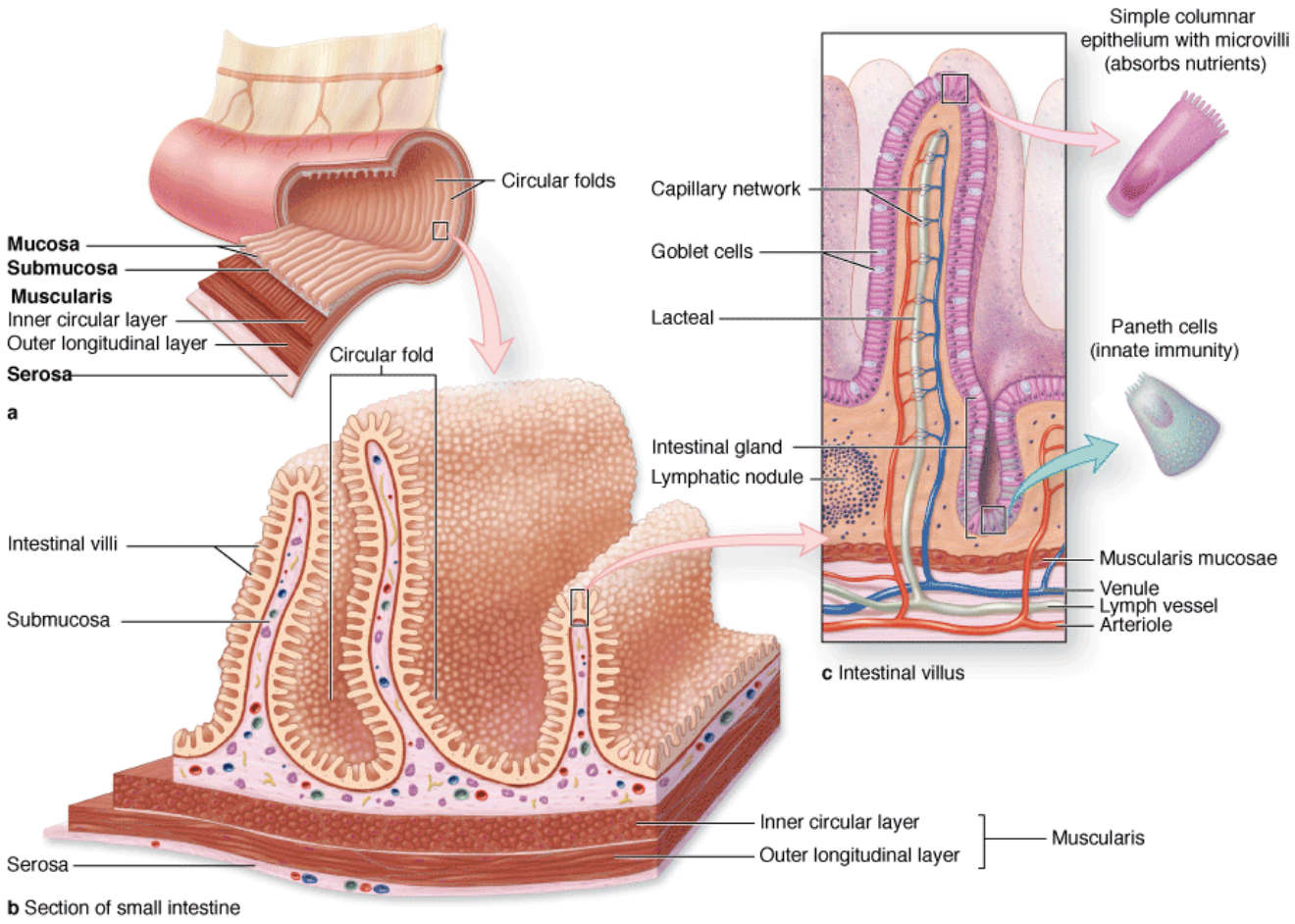
SMALL INTESTINE

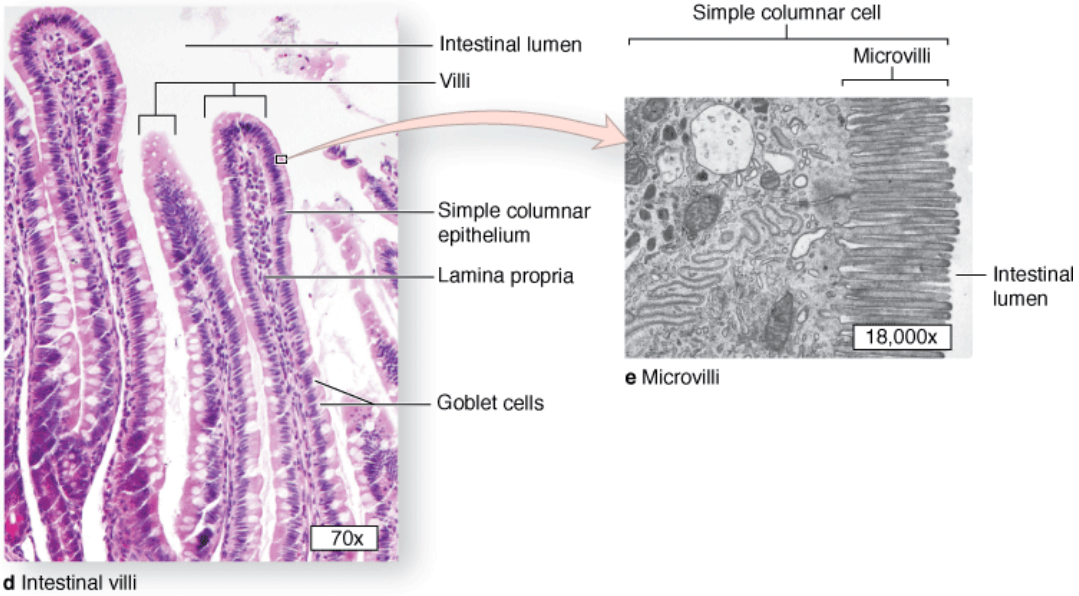
The small intestine is the site of terminal food digestion, nutrient absorption, and endocrine secretion. The processes of digestion are completed in the small intestine, where the nutrients (products of digestion) are absorbed by cells of the epithelial lining. The small intestine is relatively long—approximately 5 m—and consists of three segments: **duodenum, jejunum,** and **ileum.** These segments have many characteristics in common and will be discussed together.

Mucous Membrane

Viewed with the naked eye, the lining of the small intestine shows a series of permanent circular or semilunar folds (**plicae circulares)**, consisting of mucosa and submucosa (Figures 15–25 and 15–26), which are best developed in the jejunum. Intestinal **villi** are 0.5- to 1.5-mm-long mucosal outgrowths (epithelium plus lamina propria) and project into the lumen (Figure 15–25). In the duodenum they are leaf-shaped, but gradually assume fingerlike shapes moving toward the ileum. Villi are covered by a simple columnar epithelium of **absorptive cells** and **goblet cells**.

Figure 15–25.

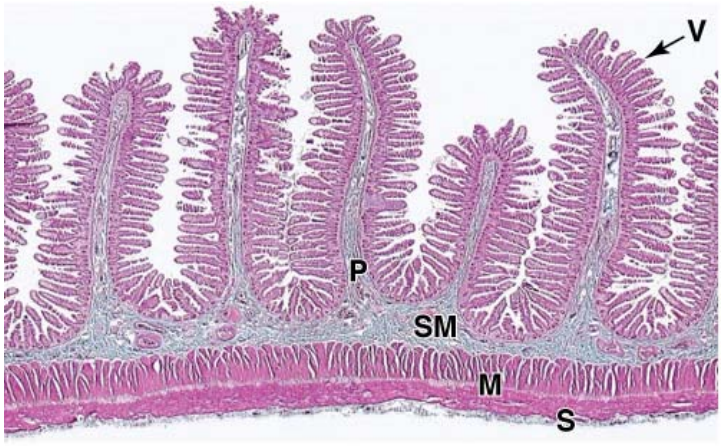




Absorptive surface of the small intestine.

(a): The mucosa and submucosa are the inner two of the gut's four concentric layers. **(b):** They form circular folds or plicae circulares, which increase the absorptive area. **(c, d):** They are lined by a dense covering of finger-like projections called villi**.** Internally each villus contains lamina propria connective tissue with microvasculature and lymphatics called **lacteals**. Villi are covered with a simple columnar epithelium composed of absorptive enterocytes and goblet cells. **(e):** At the apical cell membrane of each enterocyte are located dense **microvilli,** which serve to increase greatly the absorptive surface of the cell. Between the villi the covering epithelium invaginates to form short tubular intestinal glands or crypts, which include stem cells for the epithelium and Paneth cells which prevent intestinal flora from becoming concentrated in these glands where damage to the stem cells could occur.

Figure 15–26.

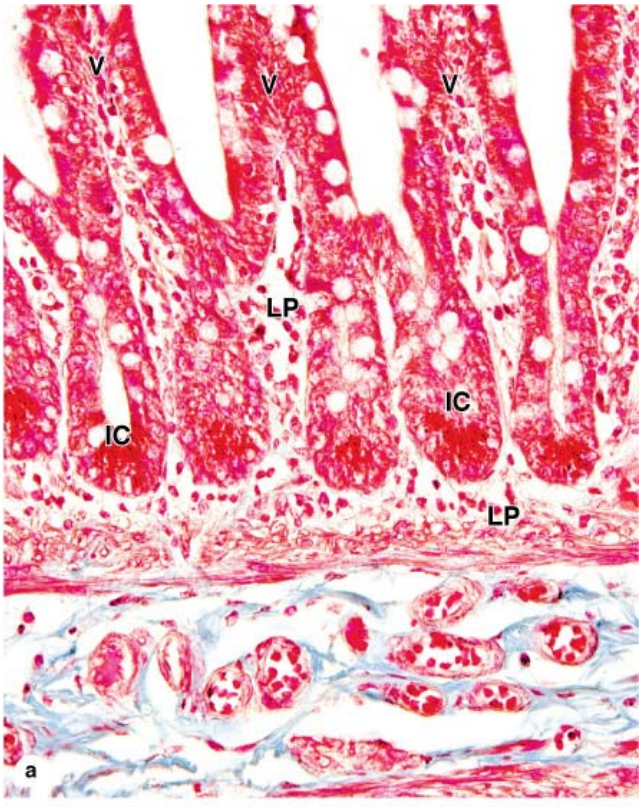


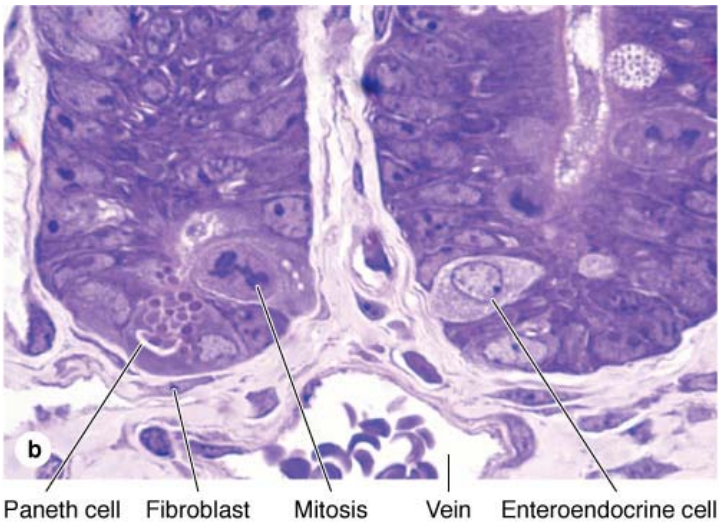
Plicae ciculares (folds) of the jejunum.

The mucosa and submucosa (SM) of the small intestine form distinct projecting folds called plicae (P), which encircle or spiral around the inner circumference and are best developed in the jejunum. On each fold the mucosa forms a dense covering of projecting structures called villi (V). In this longitudinal section the two layers of the muscularis (M) are clearly distinguished. The inner layer has smooth muscle encircling the submucosa; the outer layer runs lengthwise just inside the serosa (S), the gut's outer layer. This arrangement of smooth muscle provides for strong peristaltic movement of the gut's contents. X12. H&E.

Between the villi are small openings of short tubular glands called **intestinal crypts** or **crypts of Lieberkühn** (Figure 15–27). The epithelium of each villus is continuous with that of the intervening glands, which contain differentiating absorptive and goblet cells, Paneth cells, enteroendocrine cells, and stem cells that give rise to all these cell types.

Figure 15–27.



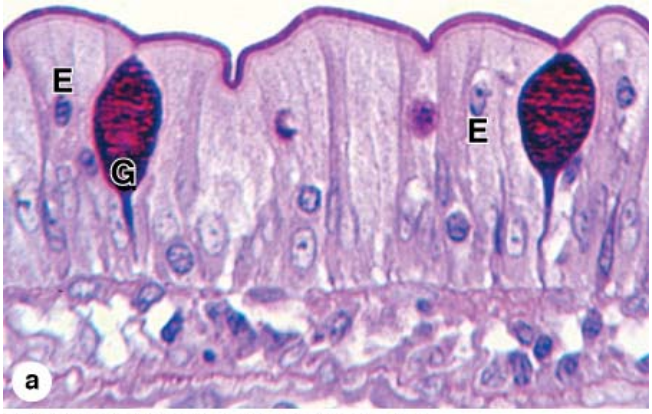


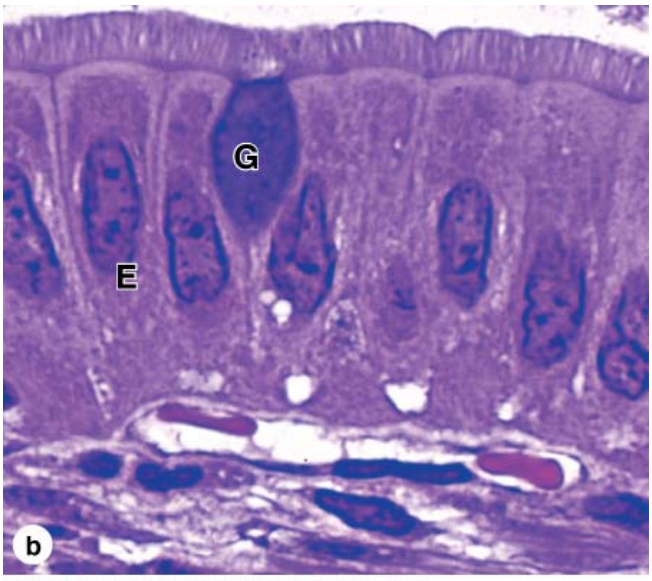
Intestinal crypts or glands.

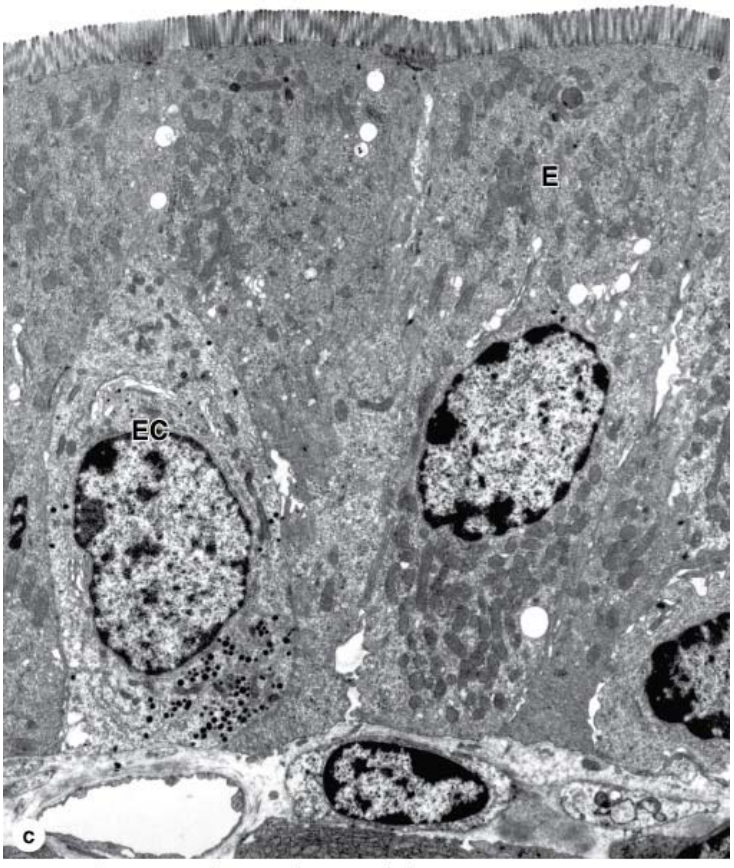
(a): Between villi (V) throughout the small intestine, as seen in this micrograph, the covering epithelium invaginates into the lamina propria (LP) to form short tubular glands called intestinal glands or intestinal crypts (IC). The lining near the openings of the crypts contains a population of stem cells for the entire epithelial lining of the small intestine. Daughter cells slowly move with the growing epithelium out of the crypts, differentiating as goblet cells, enterocytes, and enteroendocrine cells. These cells continue to move up each villus and within a week are shed at the tip, with billions shed throughout the small intestine each day. At the base of the crypts are Paneth cells, derived from the same stem cell population, which contain eosinophilic secretory granules. X200. H&E. **(b):** Micrograph of a plastic section showing two crypts in which other cells can be distinguished, including a paler staining enteroendocrine cell, cells in mitosis, and cells differentiating as enterocytes and goblet cells. X400. PT.

Enterocytes, the absorptive cells, are tall columnar cells, each with an oval nucleus in the basal half of the cell (Figure 15–28). At the apex of each cell is a homogeneous layer called the **striated** (or **brush**) **border**. When viewed with the electron microscope, the striated border is seen to be a layer of densely packed **microvilli** (Figures 15–25e and 15–28c). As discussed in Chapter 4, each microvillus is a cylindrical protrusion of the apical cytoplasm approximately 1 μm tall and 0.1 μm in diameter containing actin filaments and enclosed by the cell membrane. Each absorptive cell is estimated to have an average of 3000 microvilli and 1 mm^2 of mucosa contains about 200 million of these structures. Microvilli greatly increase the area of contact between the intestinal surface and the nutrients, a function also of the plicae and villi, which is an important feature in an organ specialized for absorption. It is estimated that plicae increase the intestinal surface three-fold, the villi increase it 10-fold, and the microvilli increase it 20-fold. Together, these processes are responsible for a 600-fold increase in the intestinal surface, resulting in a total absorptive area of 200 m^2!

Figure 15–28.





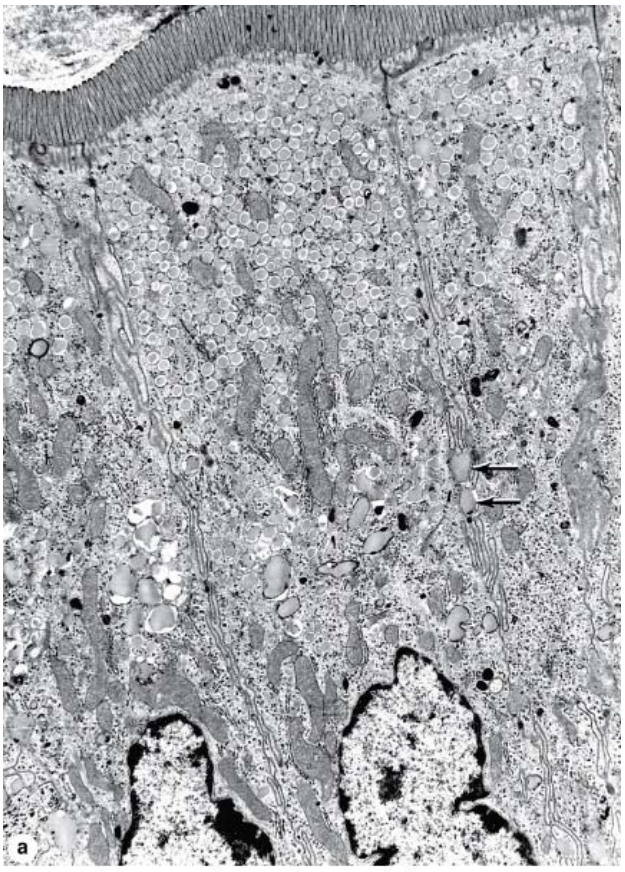


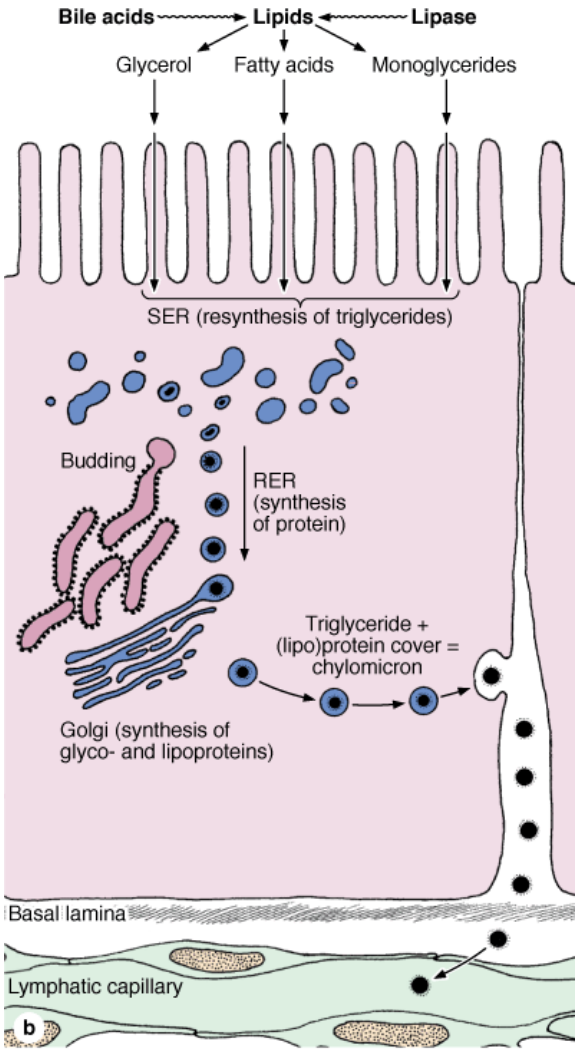
Cells covering the villi.

(a): The columnar epithelium that covers intestinal villi consists mainly of the tall absorptive enterocytes (E). The apical ends of these cells are joined and covered by a brush border of microvilli. Covered by a coating of glycoproteins, the brush border, along with the mucus-secreting goblet cells (G), stains with carbohydrate staining methods. Other cells of the epithelium are scattered enteroendocrine cells, which are difficult to identify in routine preparations, and various immune cells such as intraepithelial lymphocytes. The small spherical nuclei of lymphocytes can be seen between the enterocytes. X200. PAS-hematoxylin. **(b):** At higher magnification individual microvilli of enterocytes are better seen and the striated appearance of the border is apparent. **(c):** TEM shows microvilli and densely packed mitochondria of enterocytes, and enteroendocrine cells (EC) with secretory granules can be distinguished along the basal lamina. X1850.

Enterocytes absorb the nutrient molecules produced by digestion. Disaccharidases and peptidases secreted by these cells and bound to the microvilli hydrolyze the disaccharides and dipeptides into monosaccharides and amino acids that are easily absorbed through active transport. Digestion of fats results from the action of pancreatic lipase and bile. In humans, most of the lipid absorption takes place in the duodenum and upper jejunum and Figure 15–29 illustrates basic aspects of lipid absorption.

Figure 15–29.





Lipid absorption and processing by enterocytes.

(a): TEM showing that enterocytes involved in lipid absorption accumulate many small lipid droplets in vesicles of the smooth ER. These vesicles fuse near the nucleus, forming larger globules that are moved laterally and cross the cell membrane to the extracellular space (arrows) for eventual uptake by lymphatic capillaries (lacteals) in the lamina propria. X5000.

(b): Diagram explaining how lipids are processed by enterocytes. Bile components in the lumen emulsify fats into lipid droplets, which are broken down further by lipases to monoglycerides and fatty acids. These compounds are stabilized in an emulsion by the action of bile acids. The products of hydrolysis diffuse passively across the microvilli membranes and are collected in the cisternae of the smooth ER, where they are resynthesized as triglycerides. Processed through the RER and Golgi, these triglycerides are surrounded by a thin layer of proteins and packaged in vesicles containing chylomicrons (0.2–1 μm in diameter) of lipid complexed with protein. Chylomicrons are transferred to the lateral cell membrane, secreted by exocytosis, and flow into the extracellular space in the direction of the lamina propria, where most enter the lymph in lacteals. (Figure 15–29a, with permission, from Robert R. Cardell, Jr, Department of Cancer and Cell Biology, University of Cincinnati College of Medicine.)

MEDICAL APPLICATION

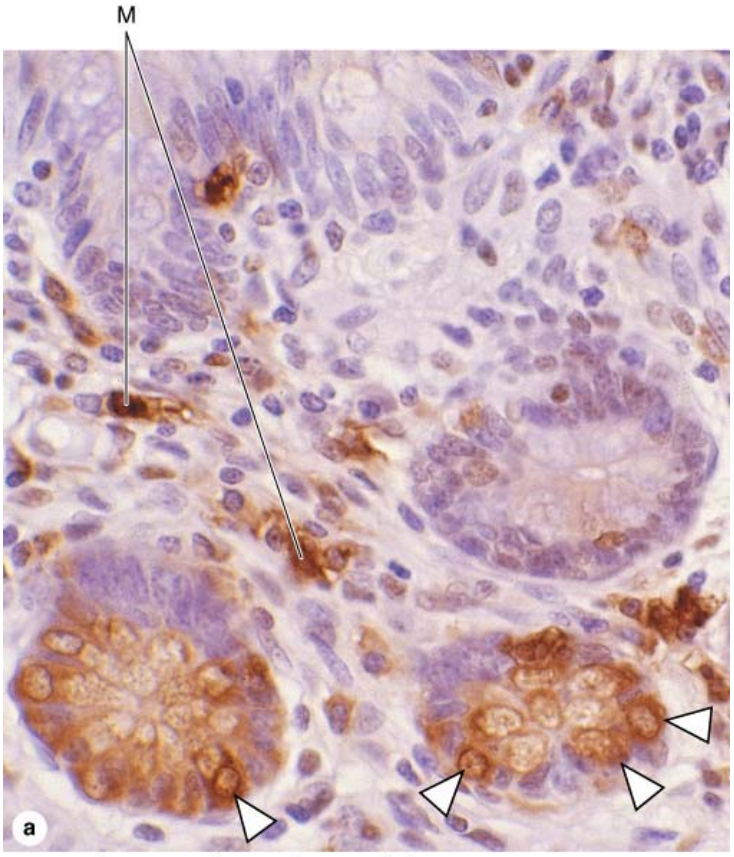
Deficiencies of disaccharidases have been described in human diseases characterized by digestive disturbances. Some of the enzymatic deficiencies seem to be of genetic origin.

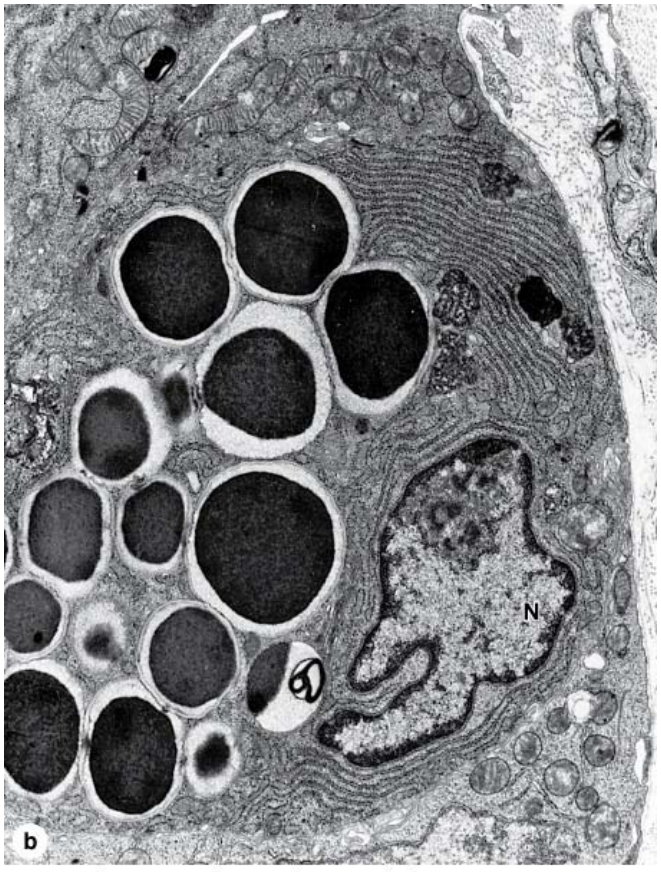
The absorption of nutrients is also greatly hindered in disorders marked by atrophy of the intestinal mucosa caused by infections or nutritional deficiencies, producing the **malabsorption syndrome**.

Goblet cells are interspersed between the absorptive cells (Figures 15–25 and 15–28). They are less abundant in the duodenum and more numerous in the ileum. These cells produce glycoprotein mucins that are hydrated and cross-linked to form mucus, whose main function is to protect and lubricate the lining of the intestine.

Paneth cells, located in the basal portion of the intestinal crypts below the stem cells, are exocrine cells with large, eosinophilic secretory granules in their apical cytoplasm (Figures 15–27 and 15–30). Paneth cell granules undergo exocytosis to release lysozyme, phospholipase A2, and hydrophobic peptides called defensins, all of which bind and breakdown membranes of microorganisms and bacterial walls. Paneth cells have an important role in innate immunity and in regulating the microenvironment of the intestinal crypts.

Figure 15–30.





Paneth cells.

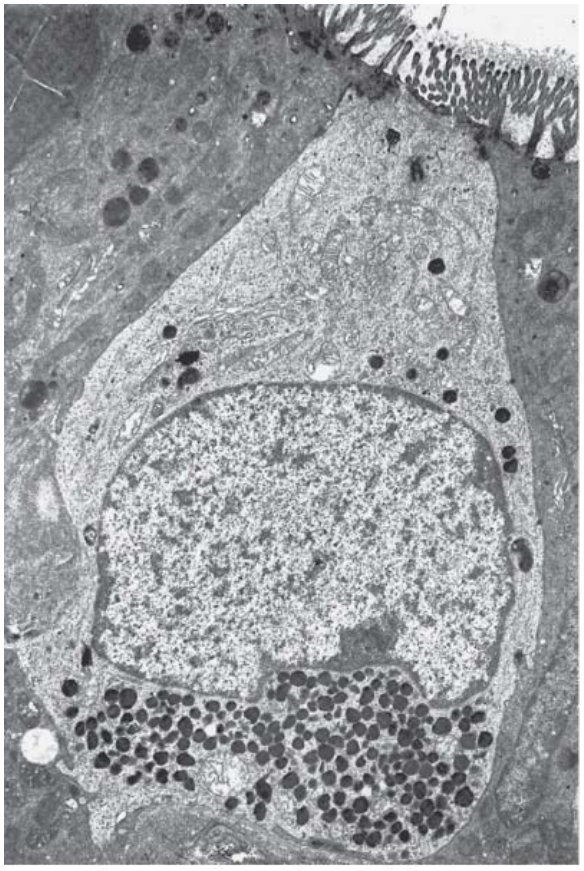
Secretory Paneth cells lie at the base of each intestinal crypt, below the level of the stem cells from which they and cells covering the villi all arise. **(a):** Micrograph of Paneth cell granules are shown immunohistochemically to contain lysozyme (arrowheads), which is also present in macrophages (M). X100.

(b): TEM shows that a Paneth cell has a prominent nucleolus in the basal nucleus (N), abundant rough ER, and large secretory granules in which the protein cores are surrounded by halos of polysaccharide-rich material. Paneth cells are key components of the gut's innate immunity, secreting into the crypt lumens

enzymes and peptides called defensins that prevent microorganisms from permanently lodging in the crypts and affecting stem cell and differentiative activities. X3000.

Enteroendocrine cells are present in varying numbers throughout the length of the small intestine, secreting various peptides (Table 15–1) and representing part of the widely distributed **diffuse neuroendocrine system** (Chapter 20). Upon stimulation these cells release their secretory granules by exocytosis and the hormones may then exert paracrine (local) or endocrine (blood-borne) effects. Polypeptide-secreting cells of the digestive tract fall into two classes: a "closed" type, in which the cellular apex is covered by neighboring epithelial cells (Figures 15–24 and 15–28) and an "open" type, in which the apex of the cell has microvilli and contacts the lumen (Figure 15–31). Peptides produced have both endocrine and paracrine effects, which include the control of peristalsis, regulation of secretions necessary for food digestion, and the sense of being satiated after eating.

Figure 15–31.



Enteroendocrine cell.

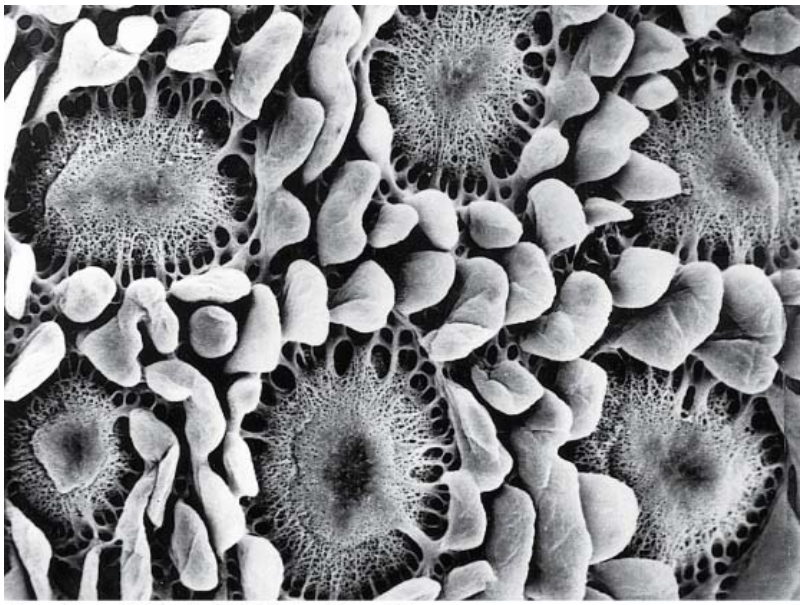
TEM of an open type enteroendocrine cell in the epithelium of the duodenum showing microvilli at its apical end in contact with the lumen. The microvilli have components of nutrient-sensing and signal transduction systems similar in some components to those of taste bud gustatory cells. Activation of these cells by nutrients triggers the release at the basolateral membranes of peptide factors, including satiation peptides, which diffuse through extracellular fluid to enter capillaries (endocrine) or to bind receptors on nearby nerve terminals, smooth muscle fibers, or other cells (paracrine). Hormones from the various enteroendocrine cells act in a coordinated manner to control gut motility, regulate secretion of enzymes, HCl, bile and other components for digestion, and produce the sense of satiety in the brain. X6900. (With permission, from A.G.E. Pearse, Department of Histochemistry, Royal Postgraduate Medical School, London.)

MEDICAL APPLICATION

The hormone secretin, produced by enteroendocrine cells of the small intestine, was the very first hormone to be discovered. Two brothers-in-law, William Bayliss and Ernest Starling, working at University College London in 1900 observed that the factor caused the pancreas to secrete its alkaline digestive fluid and they named it "secretin." They decided further to call secretin a "hormone," from the Greek verb hormaein, "to excite or set in motion." Since that time hormones purified from tissue or made synthetically have had an enormous impact in treating innumerable medical disorders.

M (**microfold**) **cells** are specialized epithelial cells in the ileum overlying the lymphoid follicles of Peyer patches. As discussed in Chapter 14, these cells are characterized by the presence of basal membrane invaginations or pockets containing many intraepithelial lymphocytes and antigen-presenting cells (Figure 14–16). M cells selectively endocytose antigens and transport them to the underlying macrophages and lymphocytes, which then migrate to lymph nodes where immune responses to foreign antigens are initiated. M cells thus serve as sampling stations where material in the lumen of the gut is transferred to immune cells of the MALT in the lamina propria. The basement membrane under the M cells is porous, facilitating transit of cells between the lamina propria and the pockets of M cells (Figure 15–32).

Figure 15–32.



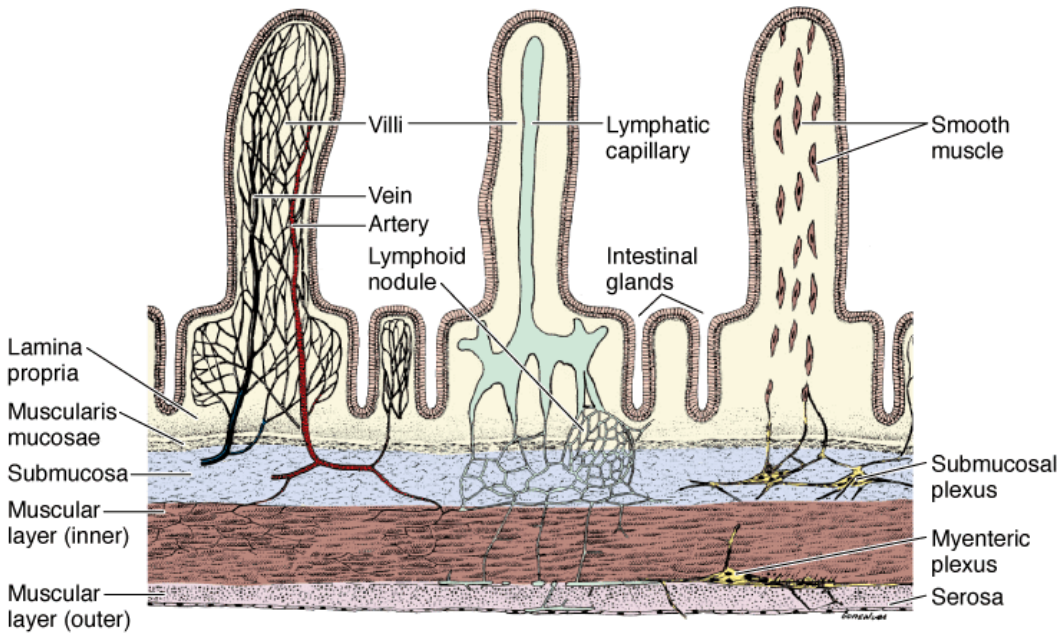
Ultrastructure of basement membrane at Peyer patches.

In the ileum of the small intestine are specialized regions of mucosa called Peyer patches, which are important parts of the mucosa-associated lymphoid tissue (MALT) in the wall of the gut. Between the villi in these regions are groups of M cells which selectively sample the lumen's contents and transfer antigens to underlying cells of the MALT. SEM of a Peyer patch after removal of the epithelial cells reveals the basement membrane. Over the broad villi the basement membrane is continuous, but over lymphoid follicles it is sieve-like, which facilitates movement of immune cells to and from the intraepithelial pockets of M cells (see Chapter 14). X1000. (With permission, from Samuel G. McClugage, Department of Cell Biology and Anatomy, Louisiana State University Health Sciences Center.)

Lamina Propria through Serosa

The lamina propria of the small intestine is composed of loose connective tissue with blood and lymph vessels, nerve fibers, and smooth muscle cells. The lamina propria penetrates the core of each intestinal villus, bringing with it microvasculature, lymphatics, and nerves (Figures 15–25 and 15–33). Smooth muscle fibers inside the villi are responsible for their rhythmic movements, which are important for efficient absorption. The muscularis mucosae also produces local movements of the villi and plicae circulares.

Figure 15–33.



Microvasculature, lymphatics, and muscle in villi.

The villi of the small intestine contain blood microvasculature (left), lymphatic capillaries called lacteals (center), and both innervation and smooth muscle fibers (right).

The proximal part of the duodenum has, primarily in its submucosa but extending into the mucosa, large clusters of branched tubular mucous glands, the **duodenal** (or **Brunner**) **glands**, with small excretory ducts opening among the intestinal crypts (Figure 15–34). The product of the glands is distinctly alkaline (pH 8.1–9.3), which neutralizes chyme entering the duodenum from the pylorus, protecting the mucous membrane and bringing the intestinal contents to the optimum pH for pancreatic enzyme action. In the ileum both the lamina propria and submucosa contain the lymphoid nodule aggregates