Subject VI DIGESTIVE SYSTEM

Program of lecture:

- Sources of development, general morpho-functional plan of digestive system.
- General morpho-functional features of alimentary canal.
- Organs of oral cavity. Lymphoepithelial ring.
- Esophagus. Stomach.
- Intestines. Histophysiology of digestion in intestines.
- Liver: development, structure, functions, blood supply.
- Pancreas. Conception about -pancreatic system

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. 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 (Fig. 1).

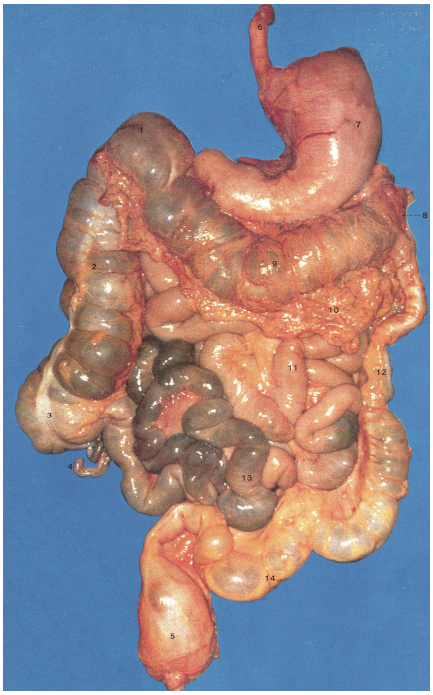


FIG. 1

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.

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 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 (Fig. 2, 3), 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. 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.

Oral Cavity

The oral cavity (Fig. 2, 3) is lined with stratified squamous epithelium, keratinized or nonkeratinized, depending on the region.

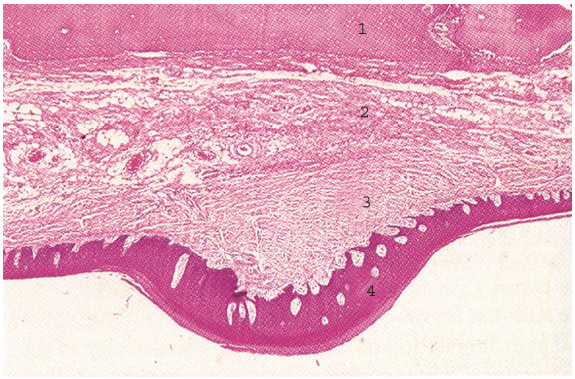


Fig.2

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.

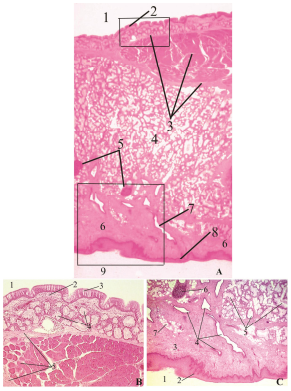


Fig.3

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 (Fig.4).

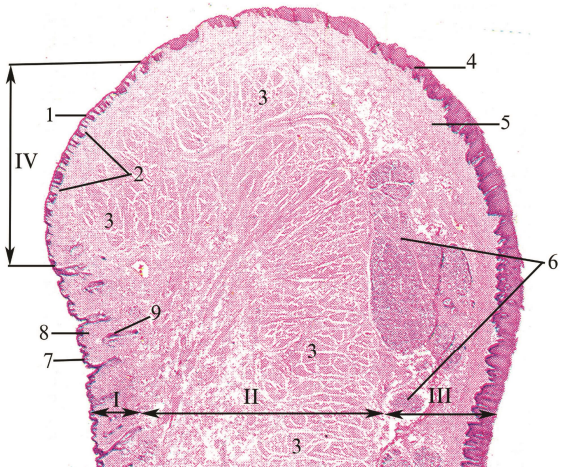


Fig.4

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

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 (Fig. 5):

Filiform papillae (Fig. 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 (Fig. 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 papilla.

Foliate papillae are poorly developed in adults, but consist of parallel ridges and furrows on the sides of the tongue, with taste buds (Fig.5, 6).

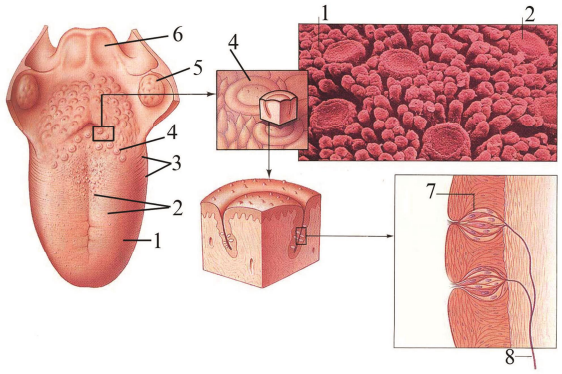


Fig.5

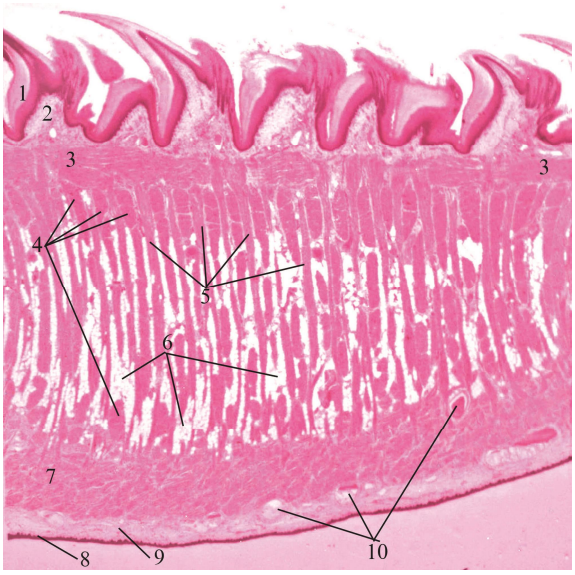


Fig.6.

Vallate (or circumvallate) papillae (Fig. 6) 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.

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 (Fig. 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

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 (Fig.7). 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 and the mucosa also has many small mucous salivary glands in its lamina propria (Fig.7, 8). The constrictor and longitudinal muscles of the pharynx are located outside this layer.

The Tonsils

The tonsils (palatine, pharyngeal, and lingual) are incompletely encapsulated aggregates of lymphoid nodules that guard the entrance to the oral pharynx. Because of their locations, the tonsils are interposed into the path of airborne and ingested antigens. They react to these antigens by forming lymphocytes and mounting an immune response.

The bilateral palatine tonsils are located at the boundary of the oral cavity and the oral pharynx, between the palatoglossal and the palatopharyngeal folds. The deep aspect of each palatine tonsil is isolated from the surrounding connective tissue by a dense, fibrous capsule. The superficial aspect of the tonsils is covered by a stratified squamous nonkeratinized epithelium that dips into the 10 to 12 deep crypts that invaginate the tonsilar parenchyma. The crypts frequently contain food debris, desquamated epithelial cells, dead leukocytes, bacteria, and other antigenic substances (Fig.7).

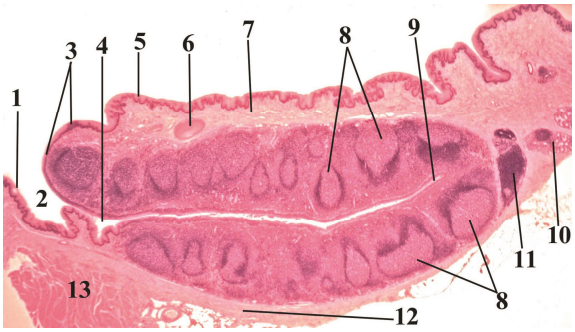


Fig.7

The single pharyngeal tonsil is in the roof of the nasal pharynx. It is similar to the palatine tonsils, but its incomplete capsule is thinner. Instead of crypts, the pharyngeal tonsil

has shallow, longitudinal infoldings called pleats. Ducts of seromucous glands open into the base of the pleats. Its superficial surface is covered by a pseudostratified ciliated columnar epithelium that is interspersed with patches of stratified squamous epithelium (Fig.8).

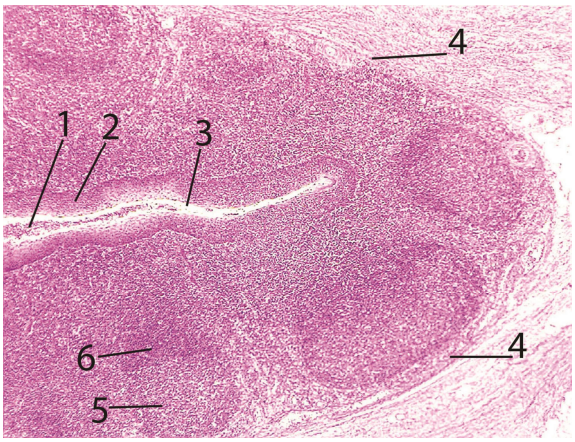


Fig.8

Teeth

In the adult human there are normally 32 permanent teeth, arranged in two bilaterally symmetric arches in the maxillary and mandibular bones (Fig. 9). 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.

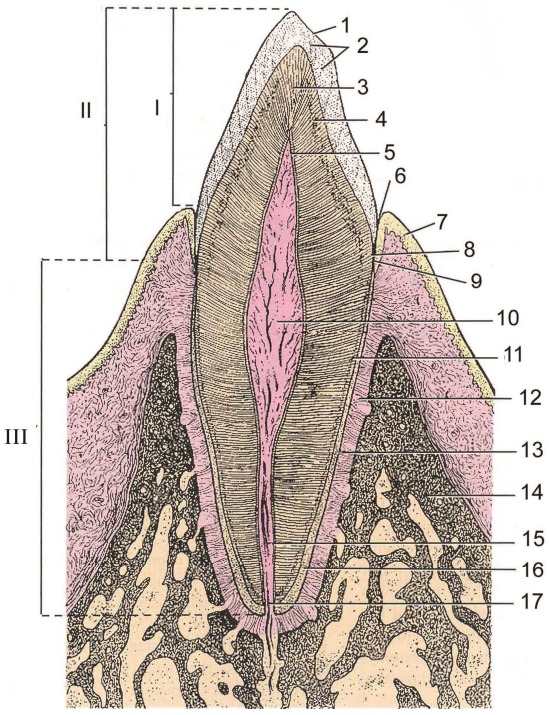


Fig.9

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 (Fig. 9).

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 (Fig. 10). 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. Mineralization of the predentin matrix involves matrix vesicles in a process similar to that in osteoid. Long, slender apical odontoblast processes lie within dentinal tubules (Fig.10) 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 (Fig.9). Odontoblasts remain active in predentin secretion into adult life, gradually reducing the size of the pulp cavity. 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 (Fig.9). The different stimuli can affect fluid inside dentinal tubules, stimulating these nerve fibers located near odontoblast processes. 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. 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.

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. 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.

Periodontium

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.

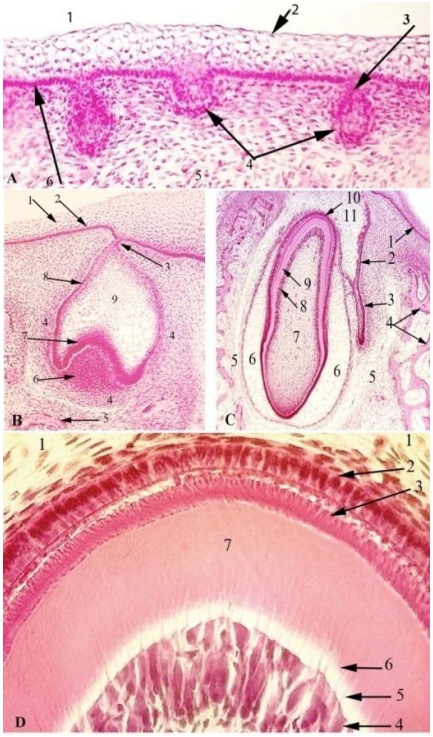
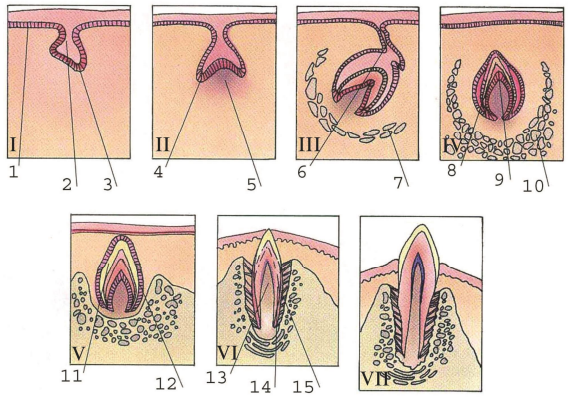


Fig.10

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 (Fig.10, 11).

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 (Fig. 9, 10, 11).



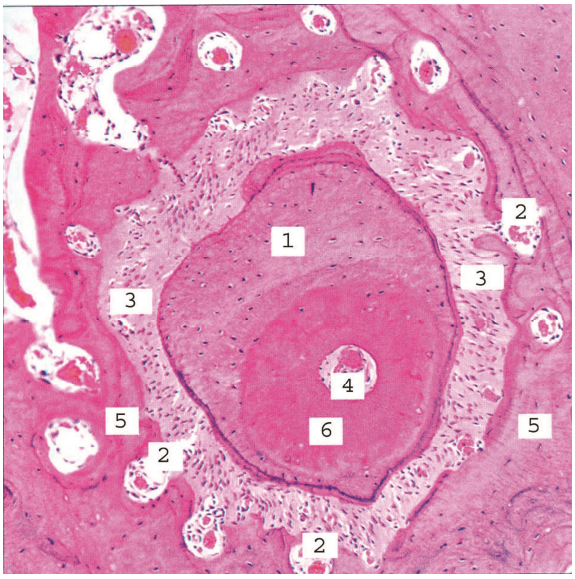


Fig.11

Enamel organ at a later stage shows 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 Fig. 11. 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 (Fig.12).

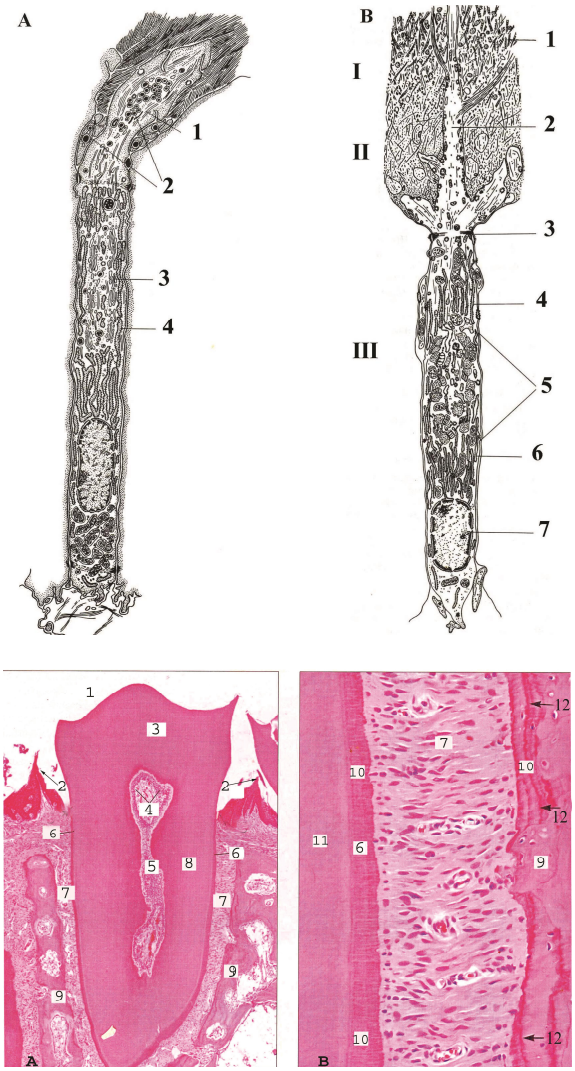
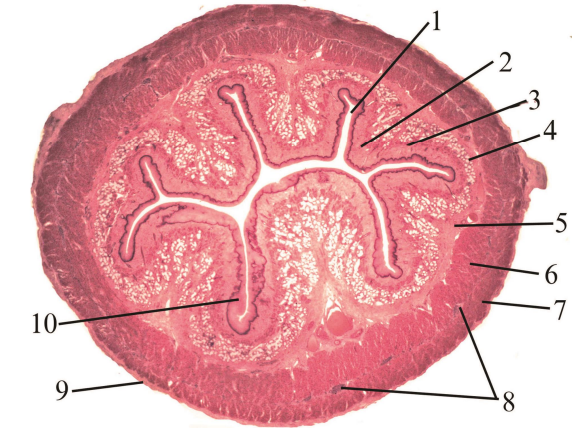


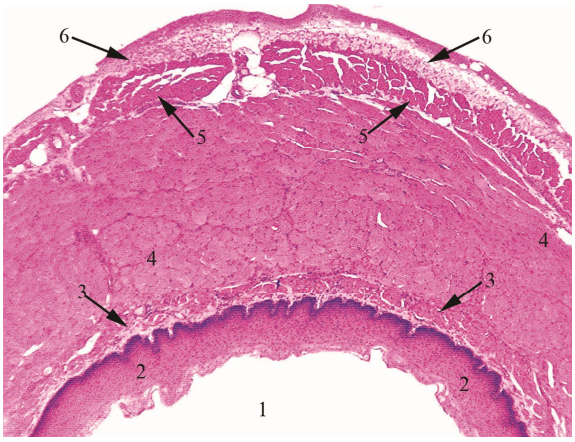
Fig. 12

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 (Fig. 13). 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.

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 (Fig. 13) 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 (Fig 13).





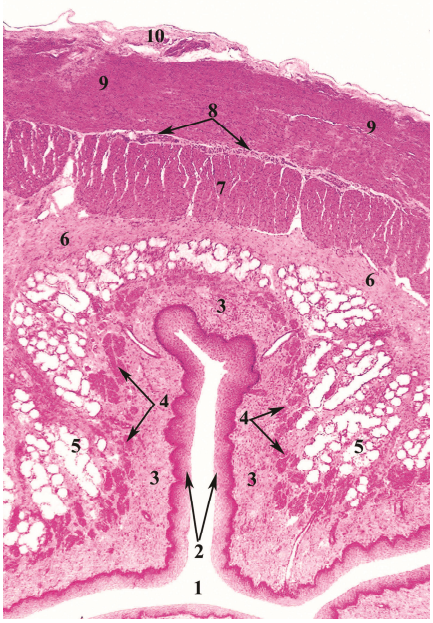


Fig.13

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 (Fig. 14). 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.

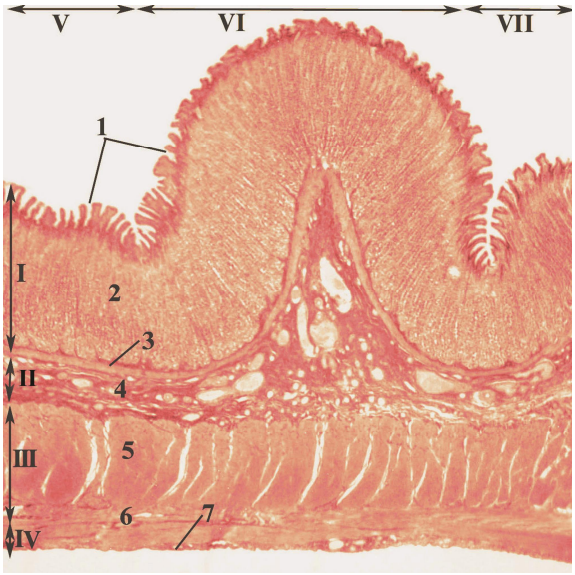


FIG. 14

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 (Fig. 15, 16). 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.

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 (Fig. 16, 17). 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.

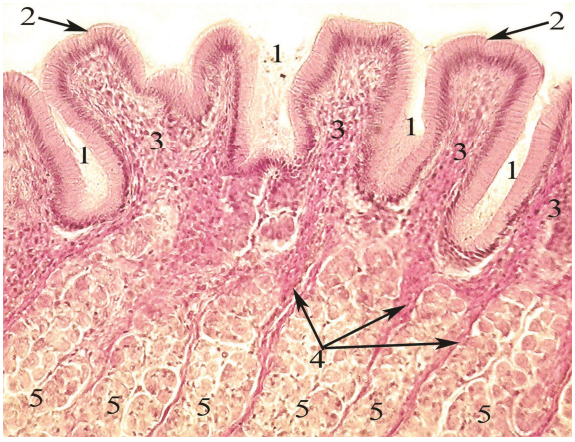


FIG. 15

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.

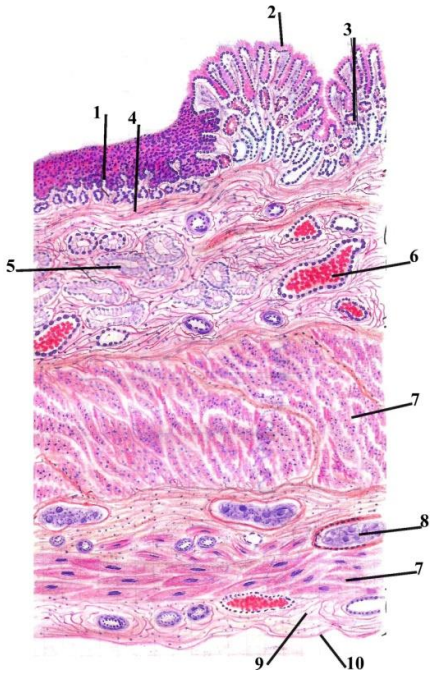


Fig.16

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 (Fig.16). 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 (Fig. 17). 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 (Fig.15).

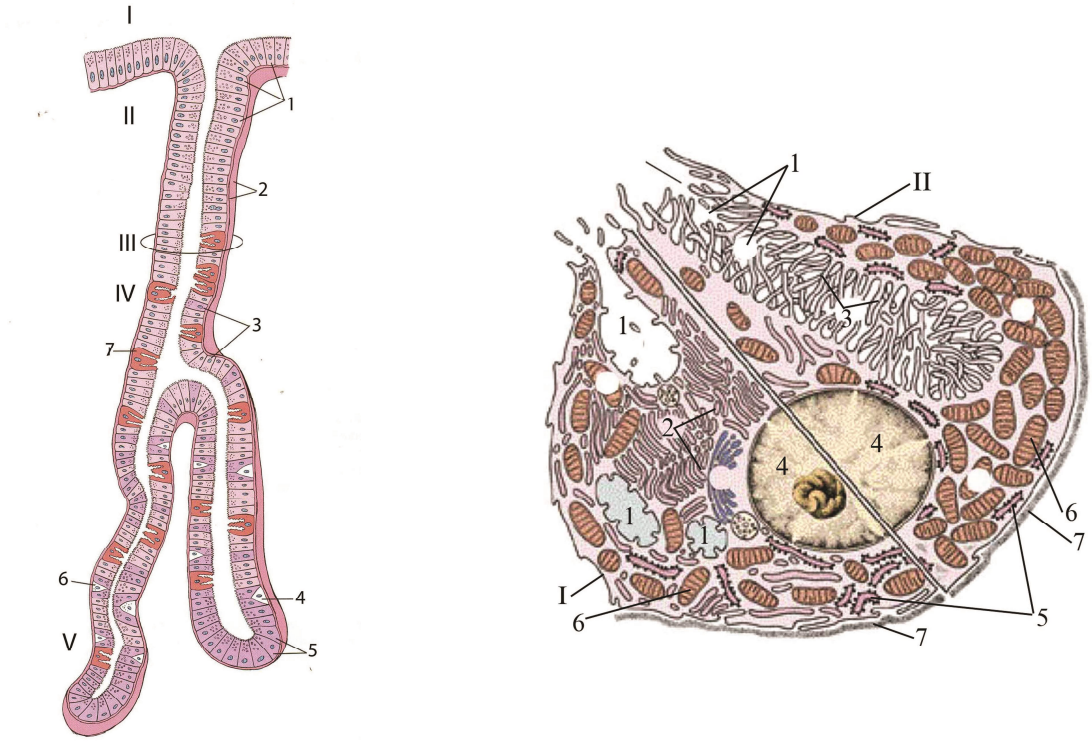


Fig. 17

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. 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 (Fig.15); 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 (Fig. 16).

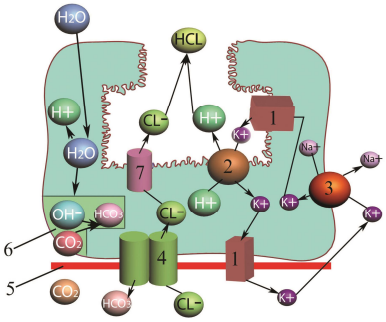


Fig. 18

Gastric glands.

Throughout the fundus and body regions of the stomach the gastric pits lead to glands with various cell types. 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 (Fig. 16). Around these tubular glands are various cells and microvasculature in connective tissue (Fig. 15).

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 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 (Fig. 18). 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. 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^+. 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 (Fig. 17, 18).

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 (Fig. 19), 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. 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 (Fig. 19).

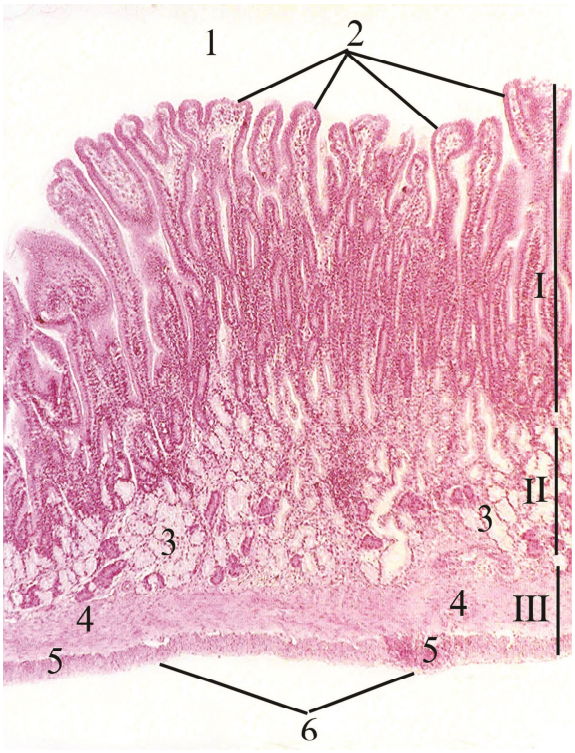


Fig. 19

Between the villi are small openings of short tubular glands called intestinal crypts or crypts of Lieberkühn (Fig.20). 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.

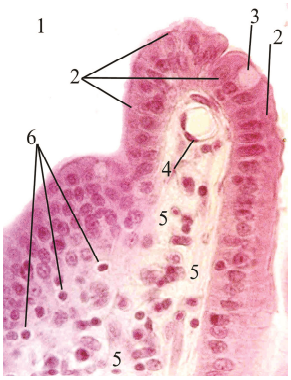
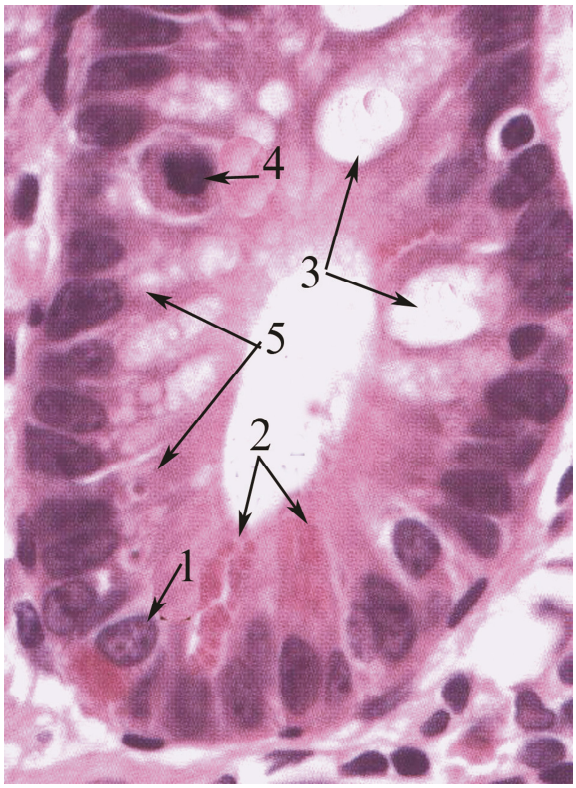


Fig. 20

Enterocytes, the absorptive cells, are tall columnar cells, each with an oval nucleus in the basal half of the cell. 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 (Fig. 21). Each microvillus is a cylindrical protrusion of the apical cytoplasm approximately 1 m tall and 0.1 m 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 $m^{2.}$.



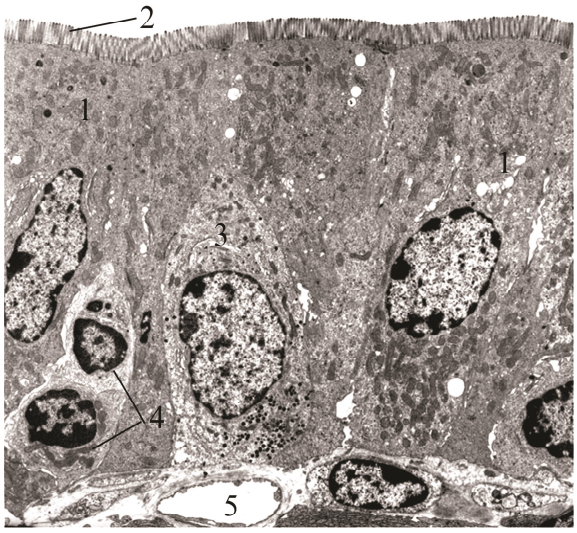


Fig.21

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 (Fig. 22).

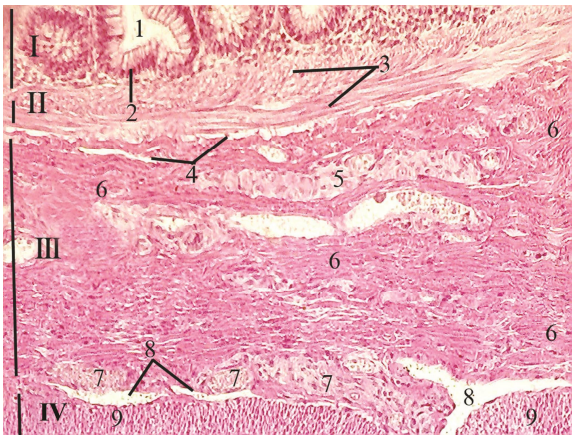


Fig. 22

Enteroendocrine cells are present in varying numbers throughout the length of the small intestine, secreting various peptides and representing part of the widely distributed diffuse neuroendocrine system. 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 and an "open" type, in which the apex of the cell has microvilli and contacts the lumen. 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.

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. 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.

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. 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 known as Peyer patches, an important component of the MALT (Fig. 23, 24).

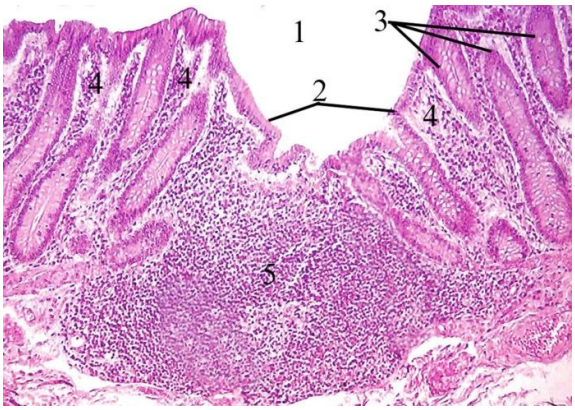


Fig. 23

The muscularis is well developed in the small intestine, composed of an internal circular layer and an external longitudinal layer, and is covered by a thin serosa with mesothelium.

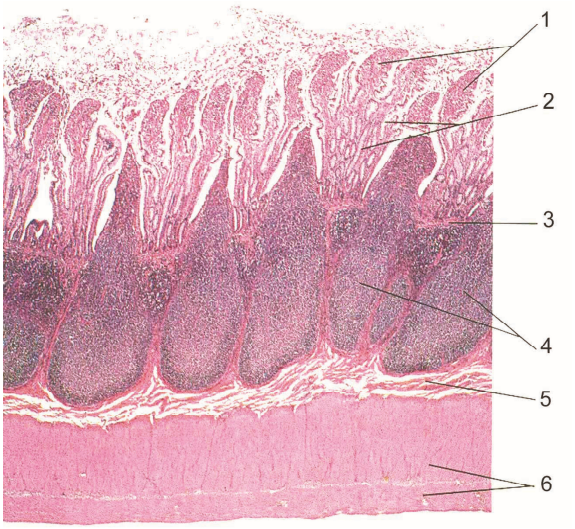


Fig. 24

Vessels and Nerves

The blood vessels that nourish the intestine and remove absorbed products of digestion penetrate the muscularis and form a large plexus in the submucosa (Fig. 22). From the submucosa, branches extend through the muscularis mucosae and lamina propria and into the villi. Each villus receives, according to its size, one or more branches that form a capillary network just below its epithelium. At the tips of the villi, one or more venules arise from these capillaries and run in the opposite direction, reaching the veins of the submucosal plexus. The lymph vessels of the intestine begin as closed tubes in the cores of villi. These capillaries (lacteals), despite being larger than the blood capillaries, are often difficult to observe because their walls are so close together that they appear to be collapsed. Lacteals run to the region of lamina propria above the muscularis mucosae, where they form a plexus. From there they are directed to the submucosa, where they surround lymphoid nodules. Lacteals anastomose repeatedly and leave the intestine along with the blood vessels. They are especially important for lipid absorption; chylomicrons of lipoprotein are preferentially taken up by lacteals rather than blood capillaries.

Another process important for intestinal function is the rhythmic movement of the villi. This movement is the result of the contraction of smooth muscle fibers running vertically from the muscularis mucosae to the tip of the villi. These contractions occur at the rate of several strokes per minute and have a pumping action on the villi that propel the lymph to the mesenteric lymphatics.

The innervation of the intestines is formed by intrinsic and extrinsic components comprising the enteric nervous system. The intrinsic component comprises many small and diffuse groups of neurons that form the myenteric (Auerbach) nerve plexus between the outer longitudinal and inner circular layers of the muscularis and the smaller submucosal (Meissner) plexus in the submucosa. The enteric nervous system contains some sensory neurons that receive information from nerve endings near the epithelial layer and in the muscularis regarding the intestinal content (chemoreceptors) and the degree of intestinal wall expansion (mechanoreceptors). Other nerve cells are effectors innervating the muscle layers and hormone-secreting cells. The intrinsic innervation formed by these plexuses is responsible for the intestinal contractions that occur even in the absence of the extrinsic innervation that modulates the activity.

Large Intestine

The large intestine or bowel consists of a mucosal membrane with no folds except in its distal (rectal) portion and no villi (Fig. 25). The mucosa is penetrated throughout its area by tubular intestinal glands lined by goblet and absorptive cells, with a small number of enteroendocrine cells. The absorptive cells or colonocytes are columnar and have short, irregular microvilli. Stem cells for the epithelium of the large bowel are located in the bottom third of each gland. The large intestine is well suited to its main functions: absorption of water, formation of the fecal mass from undigestible material, and production of mucus that lubricates the intestinal surface.

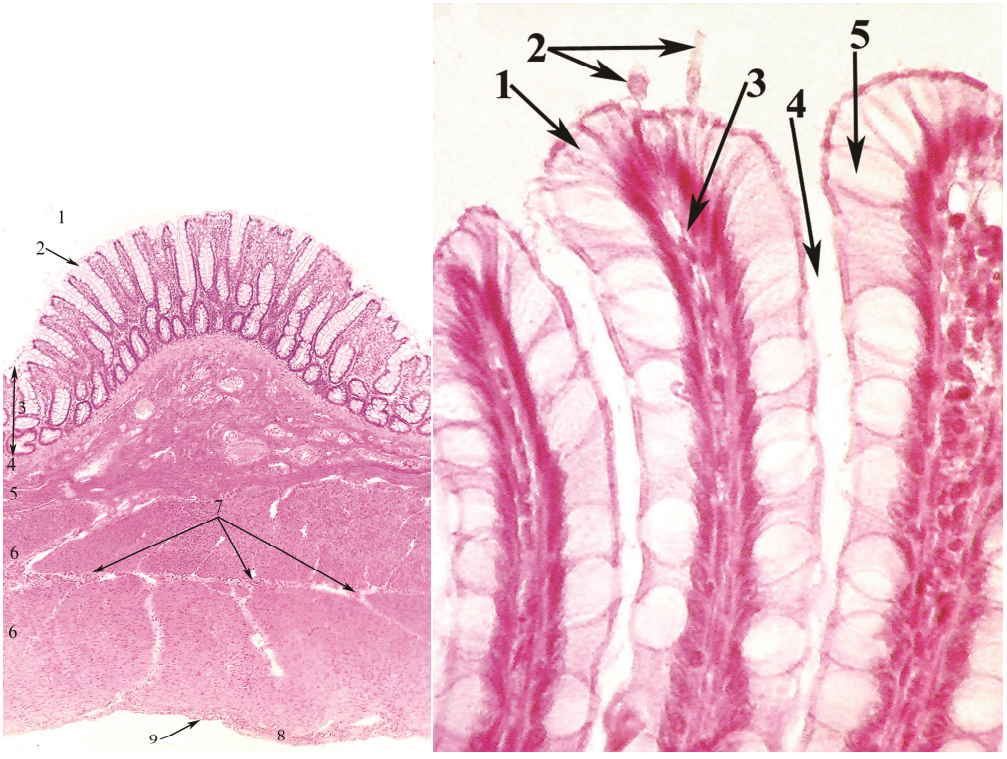


Fig.25

The lamina propria is rich in lymphoid cells and in lymphoid nodules that frequently extend into the submucosa. The richness in MALT is related to the large bacterial population of the large intestine. The muscularis comprises longitudinal and circular strands, but differs from that of the small intestine, with fibers of the outer layer gathered in three longitudinal bands called taeniae coli. Intraperitoneal portions of the colon are covered by serosa, which is characterized by small, pendulous protuberances of adipose tissue.

Near the beginning of the large intestine, the appendix is an evagination of the cecum. It is characterized by a relatively small and irregular lumen, shorter and less dense tubular glands, and no taeniae coli. Although it has no function in digestion, the appendix is a significant component of the MALT, with abundant lymphoid follicles in its wall (Fig. 25).

Appendix.

A blind evagination off the cecum, the appendix, has a very small lumen, fewer glands in its mucosa, and no taeniae coli. The laminar propria and submucosa are generally filled with lymphocytes and lymphoid follicles, making the appendix a significant part of the MALT.

Organs Associated With the Digestive Tract: Introduction

The organs associated with the digestive tract include the salivary glands, the pancreas, the liver, and the gallbladder. Products of these organs facilitate transport and digestion of food within the gastrointestinal tract. The main functions of the salivary glands are to wet and lubricate ingested food and the oral mucosa, to initiate the digestion of carbohydrates and lipids with amylase and lipase, and to secrete protective bacteriostatic substances such as the immunoglobulin IgA, lysozyme, and lactoferrin.

The pancreas produces digestive enzymes that act in the small intestine and hormones important for the metabolism of the absorbed nutrients. The liver produces bile, an important fluid in the digestion of fats. The gallbladder absorbs water from the bile and stores it in a concentrated form. The liver also plays a major role in carbohydrate and protein metabolism and inactivates and metabolizes many toxic substances and drugs. It also synthesizes most blood plasma proteins and the factors necessary for blood coagulation.

Salivary Glands

Exocrine glands in the mouth produce saliva, which has digestive, lubricating, and protective functions. With a usual pH of 6.5 6.9, saliva also has an important buffering function and in many nonhuman species is also very important for evaporative cooling. There are three pairs of large salivary glands: the parotid, submandibular, and sublingual glands (Fig. 26), in addition to minor glands in mucosa and submucosa throughout the oral cavity which secrete 10% of the total volume of saliva.

Mucous cells are somewhat more cuboidal or columnar in shape, with nuclei pressed toward the bases of the cells. They exhibit the characteristics of mucus-secreting cells, containing hydrophilic glycoprotein mucins which are important for the moistening and lubricating functions of the saliva. Mucous cells are most often organized as tubules rather than acini and produce mostly mucins.

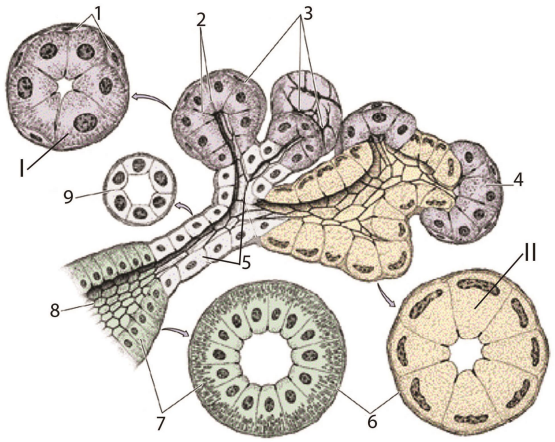


Fig. 26

Myoepithelial cells are found inside the basal lamina of the secretory units and (to a lesser extent) the initial part of the duct system. Surrounding the secretory portion myoepithelial cells are well developed and branched (and are sometimes called basket cells), whereas those associated with the initial ducts are spindle-shaped and lie parallel to the duct's length. Myoepithelial cells prevent distention of the endpiece when the lumen fills with saliva and their contraction accelerates secretion of the product.

In the intralobular duct system, secretory endpieces empty into intercalated ducts, lined by cuboidal epithelial cells, and several of these short ducts join to form striated ducts. The columnar cells of striated ducts often show radial striations extending from the cell bases to the level of the nuclei. Ultrastructurally the striations consist of infoldings of the basal plasma membrane. Numerous mitochondria are aligned parallel to the infolded membranes which contain ion transporters. Such folds greatly increase the cell surface area, facilitating ion absorption, and are characteristic of cells specialized for ion transport (Fig. 27).

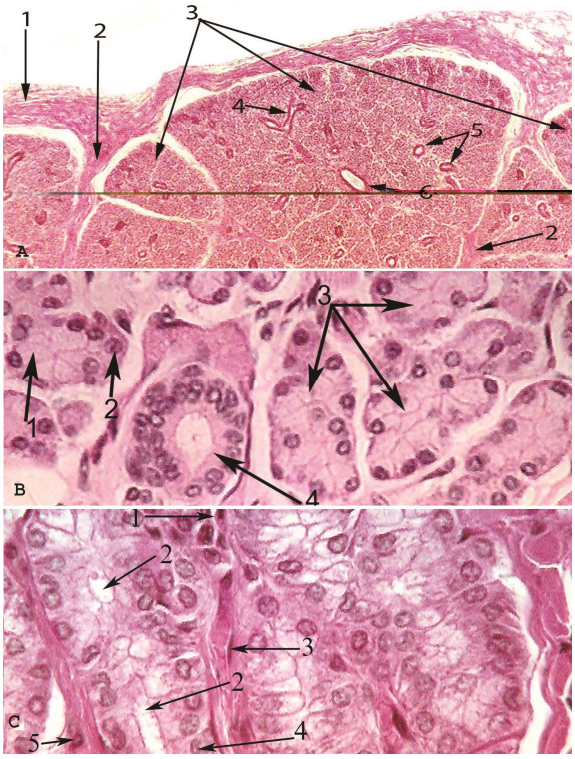


Fig. 27

In the large salivary glands, the connective tissue contains many lymphocytes and plasma cells. The plasma cells release IgA, which forms a complex with a secretory component synthesized by the epithelial cells of serous acini and intralobular ducts. The IgA-secretory complex released into the saliva resists enzymatic digestion and constitutes an immunologic defense mechanism against pathogens in the oral cavity (Fig. 28).

The striated ducts of each lobule converge and drain into ducts located in the connective tissue septa separating lobules, where they become interlobular, or excretory, ducts. They are initially lined with pseudostratified or stratified cuboidal epithelium, but more distal parts of the excretory ducts are lined with stratified columnar epithelium containing a few mucous cells. The main duct of each large salivary gland ultimately empties into the oral cavity and is lined with nonkeratinized-stratified squamous epithelium (Fig. 29).

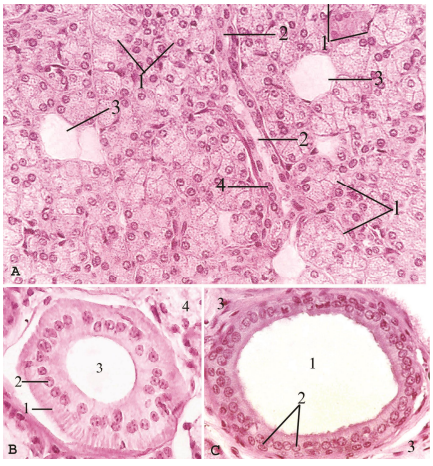


Fig. 28

Vessels and nerves enter the large salivary glands at a hilum and gradually branch into the lobules. A rich vascular and nerve plexus surrounds the secretory and ductal components of each lobule. The capillaries surrounding the secretory endpieces are very important for the secretion of saliva, which is stimulated by the autonomic nervous system. Parasympathetic stimulation, usually elicited through the smell or taste of food, provokes a copious watery secretion with relatively little organic content. Sympathetic stimulation inhibits such secretion, and produces the potential for dry mouth often associated with anxiety.

Features specific to each group of major salivary glands include the following:

Parotid gland, located in each cheek near the ear, is a branched acinar gland with secretory portions composed exclusively of serous cells surrounding very small lumens (Fig. 28). Serous cells contain secretory granules with abundant -amylase and proline-rich proteins. Amylase activity is responsible for most of the hydrolysis of ingested carbohydrates which begins in the mouth. Proline-rich proteins, the most abundant factors in parotid saliva, have antimicrobial properties and Ca^{2+} binding properties that may help maintain the surface of enamel.

Submandibular gland is a branched tubuloacinar gland, with secretory portions containing both mucous and serous cells (Fig. 29). The serous cells are the main component of this gland and are easily distinguished from mucous cells by their rounded nuclei and basophilic cytoplasm. Most of the secretory units in this gland are serous acinar, with about 10% consisting of mucous tubules capped with serous cells. Such caps are called serous demilunes. Lateral and basal membrane infoldings of the serous cells increase the ion-transporting surface area and facilitate electrolyte and water transport. In addition to -amylase and proline-rich proteins, serous cells of the submandibular gland secrete other enzymes, including lysozyme, which hydrolyzes the walls in many types of bacteria.

Sublingual gland, like the submandibular gland, is a branched tubuloacinar gland formed of serous and mucous cells. Here mucous cells predominate, with serous cells only present in demilunes on mucous tubules. The major salivary product is mucus, but cells of the serous demilunes in this gland secrete amylase and lysozyme.

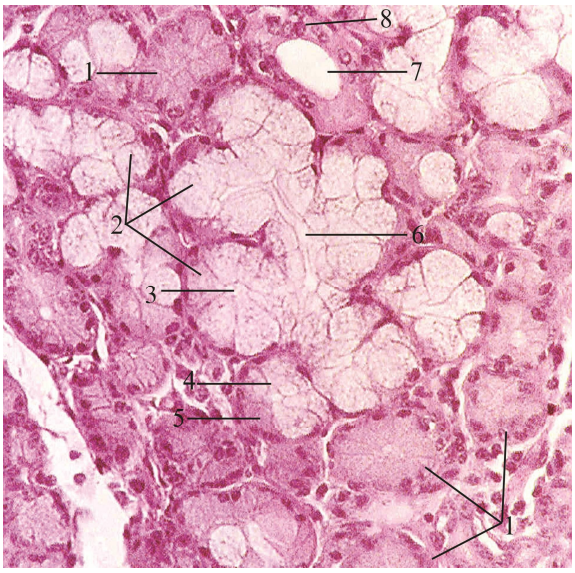


Fig. 29

Pancreas

The pancreas is a mixed exocrine-endocrine gland that produces both digestive enzymes and hormones. A thin capsule of connective tissue covers the pancreas and sends septa into it, separating the pancreatic lobules. The secretory acini are surrounded by a basal lamina that is supported by a delicate sheath of reticular fibers and a rich capillary network (Fig. 30).

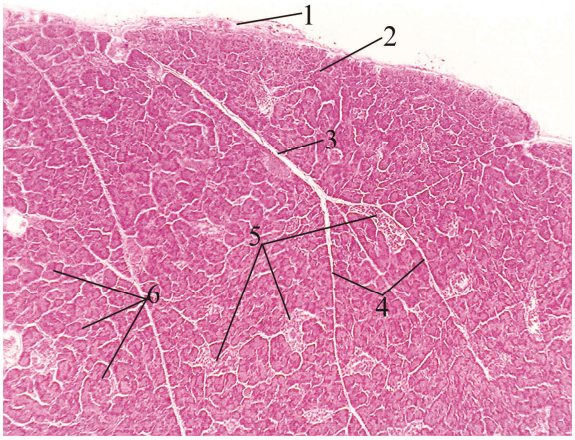


Fig. 30

The digestive enzymes are produced by cells of the larger exocrine portion and the hormones are synthesized in clusters of endocrine epithelial cells known as pancreatic islets (islets of Langerhans). The exocrine portion of the pancreas is a compound acinar gland, similar in structure to the parotid gland. The two glands can be distinguished histologically by the absence of striated ducts and the presence of the islets in the pancreas. Another characteristic detail is that in the pancreas the initial portions of intercalated ducts penetrate the lumens of the acini. Small pale-staining centroacinar cells constitute the intraacinar portion of the intercalated duct and are found only in pancreatic acini. Intercalated ducts merge to form larger interlobular ducts lined by columnar epithelium. No ducts in the pancreas are striated (Fig. 31). Each exocrine acinus of the pancreas is composed of several serous cells surrounding a very small lumen. The acinar cells are highly polarized, with a spherical nucleus, and are typical protein-secreting cells. The number of zymogen granules present in each cell varies and is maximal in animals that have fasted (Fig. 31).

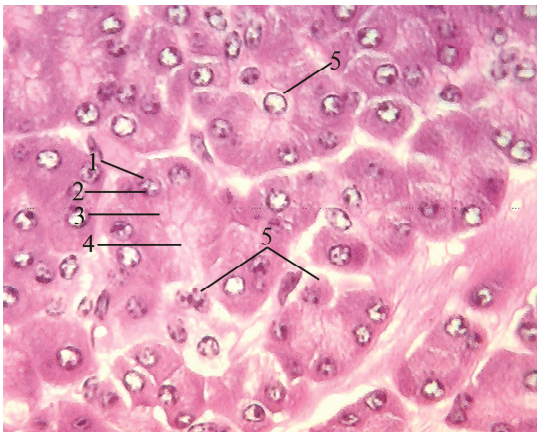


Fig. 31

The exocrine pancreas secretes 1.5 to 2 L of fluid per day. Pancreatic juice is rich in bicarbonate ions (HCO_3) and digestive enzymes, including several proteases (trypsinogens, chymotrypsinogen, proelastases, protease E, kallikreinogen, procarboxipeptidases), -amylase, lipases, and nucleases (DNAase and RNAase). The proteases are stored as inactive zymogens in the secretory granules of acinar cells. After secretion trypsinogens are cleaved and activated by enterokinase only in the lumen of the small intestine, generating trypsins which activate the other proteases in a cascade. This, along with production of protease inhibitors by the acinar cells, prevents the pancreas from digesting itself (Fig. 32).

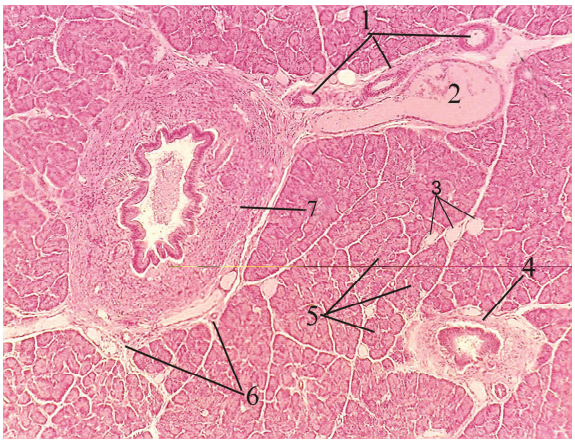


Fig. 32

Liver

Except for the skin the liver is the body's biggest organ, weighing about 1.5 kg or about 2% of an adult's body weight. With a large right lobe and smaller left lobe, it is the largest gland and is situated in the abdominal cavity beneath the diaphragm. The liver is an interface between the digestive system and the blood: the organ in which nutrients absorbed in the digestive tract are processed for use by other parts of the body. Most blood in the liver (70 80%) comes from the portal vein arising from the stomach, intestines, and spleen; the rest (20 30%) is supplied by the hepatic artery. All the materials absorbed via the intestines reach the liver through the portal vein, except the complex lipids (chylomicrons), which are transported mainly by lymph vessels. The position of the liver in the circulatory system is optimal for gathering, transforming, and accumulating metabolites from blood and for neutralizing and eliminating toxic substances in blood. The elimination occurs in the bile, an exocrine secretion of the liver that is important for lipid digestion in the gut. The liver also produces plasma proteins such as albumin, fibrinogen, and various carrier proteins (Fig. 33, 34).

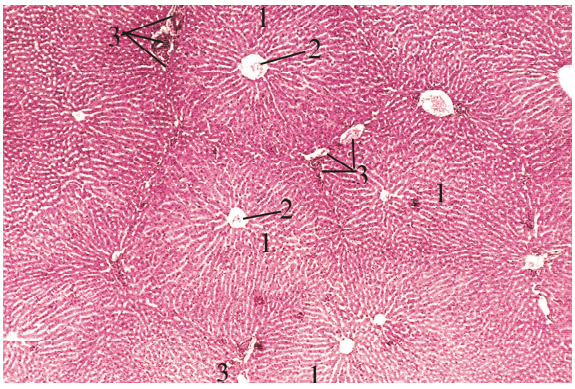


Fig. 33

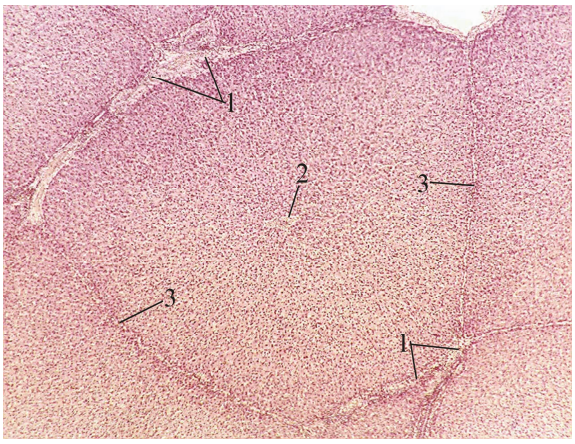
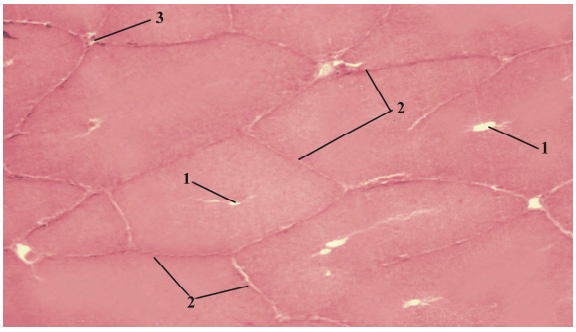


Fig. 34

Stroma

The liver is covered by a thin fibrous capsule of connective tissue that becomes thicker at the hilum, where the portal vein and the hepatic artery enter the organ and where the right and left hepatic ducts and lymphatics exit. These vessels and ducts are surrounded by connective tissue all the way to their termination (or origin) in the portal spaces between the liver lobules. At this point,, a delicate reticular fiber network surrounds and supports the liver cells and the sinusoidal endothelial cells of the liver lobules (Fig. 35).



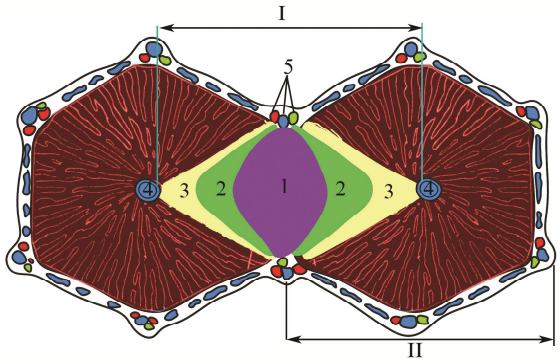


Fig. 35

Hepatic Lobules

Liver cells or hepatocytes (Gr. hepar, liver, + kytos, cell) are epithelial cells grouped in interconnected plates. Hepatocytes are arranged into thousands of small (~0.7 x 2 mm), polyhedral hepatic lobules which are the classic structural and functional units of the liver (Fig. 35, 36). Each lobule has three to six portal areas at its periphery and a venule called a central vein in its center. The portal zones at the corners of the lobules consist of connective tissue in which are embedded a venule (a branch of the portal vein), an arteriole (a branch of the hepatic artery), and a duct of cuboidal epithelium (a branch of the bile duct system) three structures called the portal triad.

The Hepatocyte

Hepatocytes are large polyhedral cells, with six or more surfaces, and typical diameters of 20 30 m. In H&E-stained sections their cytoplasm is usually eosinophilic because of the large number of mitochondria, up to 2000 per cell. Hepatocytes have large spherical nuclei with nucleoli. The cells frequently have two or more nuclei and about 50% of them are polyploid, with two, four, eight or more times the normal diploid chromosome number. Polyploid nuclei are characterized by greater size, which is proportional to their ploidy.

The surface of each hepatocyte is in contact with the wall of a sinusoid, through the perisinusoidal space, and with the surfaces of other hepatocytes. Where two hepatocytes abut, they delimit a tubular space between them known as the bile canaliculus (Fig. 36).

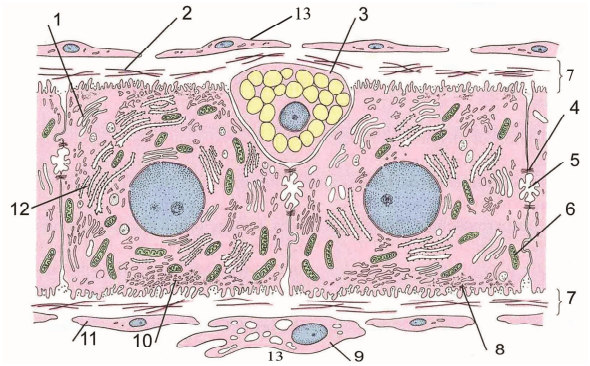


Fig. 36

The venule contains blood from the superior and inferior mesenteric and splenic veins. The arteriole contains blood from the celiac trunk of the abdominal aorta. The duct carries bile synthesized by the parenchymal cells (hepatocytes) and eventually empties into the hepatic duct. Portal areas also have nerve fibers and lymphatics. In some animals (eg, pigs), the lobules are separated from each other by a layer of connective tissue, making them easy to distinguish. In humans the lobules are in close contact along most of their length and it is more difficult to establish the exact limits between different lobules.

Hepatocytes make up each of the interconnected plates like the bricks of a wall and the plates are arranged radially around the central vein (Fig. 36, 37). From the periphery of the lobule to its center, the plates of hepatocytes branch and anastomose freely, forming a rather sponge-like structure. The spaces between these plates contain important microvascular components, the liver sinusoids. These irregularly dilated sinusoids consist only of a discontinuous layer of fenestrated endothelial cells. The endothelial cells are separated from the underlying hepatocytes by a thin, discontinuous basal lamina and a very narrow perisinusoidal space (the space of Disse), into which project microvilli of the hepatocytes for exchanges between these cells and plasma. This exchange is the key to liver function, not only because of the large number of macromolecules (eg, lipoproteins, albumin, and fibrinogen) secreted into the blood by hepatocytes but also because the liver takes up and catabolizes many of these large molecules.

Liver sinusoids are surrounded and supported by delicate sheathes of reticular fibers. Two noteworthy cells are associated with these sinusoids in addition to the endothelial cells:

Abundant specialized stellate macrophages, also known as Kupffer cells, are found between sinusoidal endothelial cells and on the luminal surface within the sinusoids, mainly near the portal areas (Fig. 35, 36). Their main functions are to break down aged erythrocytes and free heme for re-use, remove bacteria or debris that may enter the portal blood from the gut, and act as antigen-presenting cells in adaptive immunity.

In the perisinusoidal space (not the lumen) are stellate fat storing cells (or Ito cells) with small lipid droplets containing vitamin A (Fig. 37). These cells, which make up about 8% of the cells in a liver but are difficult to see in routine preparations, store much of the body's vitamin A, produce ECM components, and have a regulatory role in local immunity

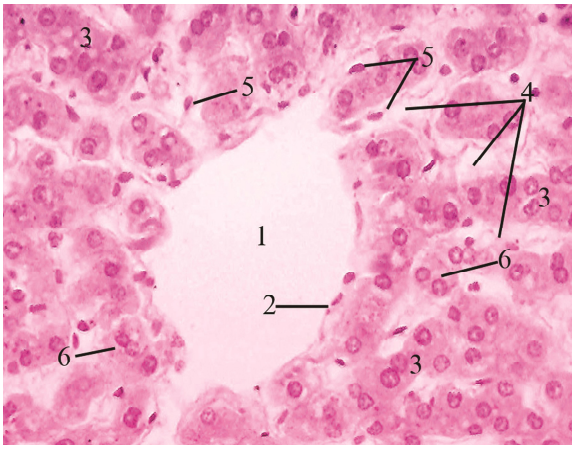


Fig. 37

Blood Supply

As an important interface for processing blood from the digestive system, the liver gets most of its blood from the portal vein, which carries nutrient-rich but oxygen-poor blood from the abdominal viscera. Oxygenated blood is brought in with the smaller portion derived from the hepatic artery. The portal system conveys blood from the pancreas, spleen, and the intestines. Nutrients are accumulated and transformed in the liver and toxic substances are neutralized and eliminated there. In the liver the portal vein branches repeatedly and sends small portal venules to the portal spaces. The portal venules branch into smaller distributing venules that run around the periphery of each lobule and lead into the sinusoids. The sinusoids run radially, converging in the center of the lobule to form the central or centrolobular vein. This vessel, like the sinusoids, has very thin walls consisting only of endothelial cells supported by a sparse population of collagen fibers. Central venules from each lobule converge into veins, which eventually form two or more large hepatic veins that empty into the inferior vena cava.

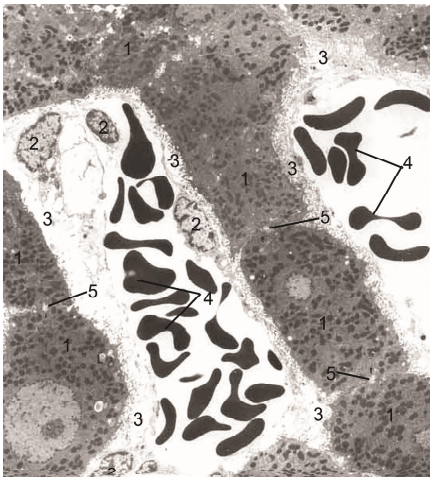


Fig. 38

The hepatic artery branches repeatedly and forms arterioles in the portal areas, some of which lead directly into the sinusoids (Fig. 38) at various distances from the portal spaces, thus adding oxygen-rich arterial blood to the portal venous blood in the sinusoids.

Blood always flows from the periphery to the center of each hepatic lobule. Consequently, oxygen and metabolites, as well as all other toxic or nontoxic substances absorbed in the intestines, reach the lobule's peripheral cells first and then the more central cells. This direction of blood flow partly explains why the properties and function of the periportal hepatocytes differ from that of the centrolobular cells. Hepatocytes near the portal areas can rely on aerobic metabolism and are often more active in protein synthesis, while the more central cells are exposed to lower concentrations of nutrients and oxygen and are more involved with detoxification and glycogen metabolism.

The canaliculi, the first portions of the bile duct system, are long spaces 1 2 m in diameter. They are limited only by the plasma membranes of two hepatocytes, which extend a small number of microvilli into their interiors. The cell membranes near these canaliculi are firmly joined by tight junctions. Gap junctions also occur between hepatocytes, allowing intercellular communication and coordination of the cells' activities. The bile canaliculi form a complex anastomosing network progressing along the plates of the hepatic lobule and terminating in the region of the portal spaces. The bile flow therefore progresses in a direction opposite to that of the blood, ie, from the center of the lobule to its periphery. Near the peripheral portal areas, bile canaliculi empty into bile ductules composed of cuboidal epithelial cells called cholangiocytes. After a short distance, these ductules cross the limiting hepatocytes of the lobule and end in the bile ducts in the portal spaces. Bile ducts are lined by cuboidal or columnar epithelium and have a distinct connective tissue sheath. They gradually enlarge and fuse, forming right and left hepatic ducts, which subsequently leave the liver.