Organs Associated with the Digestive Tract

The organs associated with the digestive tract include the ***salivary glands, the pancreas, the liver, and the gallbladder.*** The main functions of the saliva produced by salivary glands are to wet and lubricate the oral mucosa and the ingested food, to initiate the digestion of carbohydrates and lipids (by means of amylase and lingual lipase activities, respectively), and to secrete germicidal protective substances such as immunoglobulin A (IgA), lysozyme, and lactoferrin. The saliva also has a very important buffering function and forms a protective pellicle on the teeth by means of calcium-binding proline-rich salivary proteins. In some species (but not in humans), saliva is very important for evaporative cooling.

The main functions of the pancreas are to produce digestive enzymes that act in the small intestine and to secrete hormones such as insulin and glucagon into the bloodstream. Both are very important for the metabolism of the absorbed nutrients. The liver produces bile, an important fluid in the digestion of fats. It plays a major role in lipid, carbohydrate, and protein metabolism and inactivates and metabolizes many toxic substances and drugs. It also participates in iron metabolism and the synthesis of blood proteins and the factors necessary for blood coagulation. The gallbladder absorbs water from the bile and stores the bile in a concentrated form.

Salivary Glands

Saliva is a complex fluid that has digestive, lubricating, and protective functions. In addition to the small salivary glands scattered throughout the oral cavity, there are three pairs of large salivary glands: the **parotid, submandibular,** and **sublingual glands.** In humans, the minor salivary glands secrete 10% of the total volume of saliva, but they account for approximately 70% of the mucus secreted.

A capsule of connective tissue, rich in collagen fibers, surrounds the large salivary glands. The parenchyma of the glands consists of secretory end pieces and a branching duct system arranged in lobules, separated by septae of connective tissue originating from the capsule. The secretory end pieces present two types of secretory cells serous and mucous as well as the nonsecretory myoepithelial cells. This secretory portion is followed by a duct system whose components modify and conduct the saliva to the oral cavity.

Serous cells are usually pyramidal in shape, with a broad base resting on the basal lamina and a narrow apical surface with short, irregular microvilli facing the lumen. They exhibit characteristics of polarized protein-secreting cells. Adjacent secretory cells are joined together by junctional complexes and usually form a spherical mass of cells called **acinus,** with a small lumen in the center. This structure can be thought of as a grape attached to its stem; the stem corresponds to the duct system.

Mucous cells are usually cuboidal to columnar in shape; their nuclei are oval and pressed toward the bases of the cells. They exhibit the characteristics of mucus-secreting cells, containing glycoproteins important for the moistening and lubricating functions of the saliva. Most of these glycoproteins are called mucins and contain 70-80% carbohydrate moieties in their structure. Mucous cells are most often organized as **tubules,** consisting of cylindrical arrays of secretory cells surrounding a lumen. In the human **submandibular and sublingual glands,** serous and mucous cells are arranged in a characteristic pattern. The mucous cells form tubules, but their ends are capped by serous cells, which constitute the **serous demilunes**.

Myoepithelial cells, Epithelial Tissue, are found between the basal lamina and the basal plasma membrane of the cells forming secretory end pieces and intercalated ducts, which form the initial portion of the duct system. Myoepithelial cells surrounding each secretory portion, usually two to three cells per secretory unit, are well developed and branched (and are sometimes called **basket cells**), whereas those associated with intercalated ducts are spindle shaped and lie parallel to the length of the duct. These cells show several characteristics that resemble smooth muscle cells, including contractility. However, they also establish intercellular junctions among themselves and with secretory cells, such as desmosomes. Although the contraction of myoepithelial cells accelerates the secretion of saliva, their main function seems to be the prevention of end piece distention during secretion due to the increase in intraluminal pressure.

In the **duct system,** secretory end pieces empty into the **intercalated ducts,** lined by cuboidal epithelial cells. These cells have the ability to divide and differentiate into secretory or ductal cells. Several of these short intercalated ducts join to form **striated ducts**, characterized by radial striations that extend from the bases of the cells to the level of the central nuclei. When viewed in the electron microscope, the striations are seen to consist of infoldings of the basal plasma membrane with numerous elongated mitochondria that are aligned parallel to the infolded membranes; this structure is characteristic of ion-transporting cells. Intercalated and striated ducts are also called intralobular ducts because of their location within the lobule.

The striated ducts of each lobule converge and drain into ducts located in the connective tissue septae separating the 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 mucus-secreting cells. The main duct of each major salivary gland ultimately empties into the oral cavity and is lined with nonkeratinized-stratified squamous epithelium.

Vessels and nerves enter the large salivary glands at the 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 end pieces are very important for the secretion of saliva, stimulated by the autonomic nervous system.

Parasympathetic stimulation, usually through the smell or taste of food, promotes vasodilation and a copious watery secretion content. Sympathetic stimulation produces small amounts of viscous saliva, rich in organic material

Parotid Gland

The parotid gland is a branched acinar gland; its secretory portion is composed exclusively of serous cells containing secretory granules that are rich in proteins and have a high amylase activity. This activity is responsible for most of the hydrolysis of ingested carbohydrates. The digestion begins in the mouth and continues for a short time in the stomach, before the gastric juice acidifies the food and thus decreases amylase activity considerably. Intercalated and striated ducts are easily observed within the lobules, due to their length.

As in other large salivary glands, the connective tissue contains many plasma cells and lymphocytes. The plasma cells secrete IgA, which forms a complex with a **secretory component** synthesized by the serous acinar, intercalated duct, and striated duct cells. The IgA-rich secretory complex released into the saliva is resistant to enzymatic digestion and constitutes an immunological defense mechanism against pathogens in the oral cavity.

Submandibular Gland

The submandibular gland is a branched tubuloacinar gland its secretory portion contains both mucous and serous cells. The serous cells are the main component of this gland and are easily distinguished from mucous cells by their rounded nuclei and basophilic cytoplasm. In humans, 90% of the end pieces of the submandibular gland are serous acinar, whereas 10% consist of mucous tubules with serous demilunes. The presence of extensive lateral and basal membrane infoldings toward the vascular bed increases the ion-transporting surface area 60 times, facilitating electrolyte and water transport. Because of these folds, the cell boundaries are indistinct. Serous cells are responsible for the weak amylolytic activity present in this gland and its saliva. The cells that form the demilunes in the submandibular gland secrete the enzyme **lysozyme,** whose main activity is to hydrolyze the walls of certain bacteria. Some acinar and intercalated duct cells in large salivary glands also secrete lactoferrin, which binds iron, a nutrient necessary for bacterial growth. Striated ducts are easily observed in the human submandibular gland, but intercalated ducts are very short.

Sublingual Gland

The sublingual gland, like the submandibular gland, is a branched tubuloacinar gland formed of serous and mucous cells. Mucous cells predominate in this gland; serous cells are present almost exclusively on demilunes of mucous tubules. As in the submandibular

gland, cells that form the demilunes in this gland secrete lysozyme. Intralobular ducts are not as well developed as in other major salivary glands.

Minor Salivary Glands

These nonencapsulated glands are distributed throughout the oral mucosa and submucosa. Saliva is produced by small groups of secretory units and is conducted to the oral cavity by short ducts, with little modification of its content. Although variations exist, minor salivary glands are usually mucous. The small serous glands present in the posterior region of the tongue (von Ebner's glands) are the only exception . Lymphocyte agregates are commonly observed within minor salivary glands, associated with IgA secretion

Pancreas

The pancreas is a mixed exocrine and endocrine gland that produces digestive enzymes and hormones. The enzymes are stored and released by cells of the exocrine portion, arranged in acini. The hormones are synthesized in clusters of endocrine epithelial cells known as islets of Langerhans. The exocrine portion of the pancreas is a compound acinar gland, similar in structure to the parotid gland. In histological sections, a distinction between the two glands can be made based on the absence of striated ducts and the presence of the islets of Langerhans in the pancreas. Another characteristic detail is that in the pancreas the initial portions of intercalated ducts penetrate the lumens of the acini. Nuclei, surrounded by a pale cytoplasm, belong to **centroacinar cells** that constitute the intraacinar portion of the intercalated duct. These cells are found only in pancreatic acini. Intercalated ducts are tributaries of larger intralobular ducts that, in turn, form larger interlobular ducts lined by columnar epithelium, located within the connective tissue septa. There are no striated ducts in the pancreatic duct system.

The exocrine pancreatic acinus is composed of several serous cells surrounding a lumen. These cells are highly polarized, with a spherical nucleus, and are typical protein-secreting cells. The number of zymogen granules present in each cell varies according to the digestive phase and attains its maximum in animals that have fasted.

A thin capsule of connective tissue covers the pancreas and sends septa into it, separating the pancreatic lobules. The acini are surrounded by a basal lamina that is supported by a delicate sheath of reticular fibers. The pancreas also has a rich capillary network, essential for the secretory process.

The exocrine pancreas secretes 1500-3000 mL of isosmotic alkaline fluid per day containing water, ions, and several proteases (**trypsinogens 1, 2,** and **3, chymotrypsinogen, proelastases 1** and **2, protease E, kallikreinogen, procarboxypeptidases A1, A2, B1,** and **B2**),**amylase, lipases** (**triglyceride lipase, colipase,** and **carboxyl ester hydrolase**), **phospholipase** $\mathbf{A_2}$**,** and **nucleases**

(**deoxyribonuclease** and **ribonuclease**). The majority of the enzymes are stored as proenzymes in the secretory granules of acinar cells, being activated in the lumen of the small intestine after secretion. Enterokinase, an intestinal enzyme, cleaves trypsinogen to form trypsin, which then activates the other proteolytic enzymes in a cascade. This is very important for the protection of the pancreas as well as the synthesis of protease inhibitors by the acinar cells.

Pancreatic secretion is controlled mainly through two hormones **secretin** and **cholecystokinin** that are produced by enteroendocrine cells of the intestinal mucosa (duodenum and jejunum). Stimulation of the vagus nerve (parasympathetic stimulation) will also produce pancreatic secretion. Actually, the hormonal and neural systems act in concert to control pancreatic secretion.

Gastric acid (or pH < 4.5) in the intestinal lumen is a strong stimulus for secretin release. Secretin causes acinar and duct cells to add water and bicarbonate to the fluid, promoting the secretion of an abundant alkaline fluid rich in electrolytes and poor in enzyme activity. This fluid neutralizes the acidic **chyme** (partially digested food) so that pancreatic enzymes can function at their optimal neutral pH range. The release of cholecystokinin is triggered by the presence of long-chain fatty acids, gastric acid, and certain essential amino acids in the intestinal lumen. Cholecystokinin promotes secretion of a less abundant but enzyme-rich fluid acting mainly in the extrusion of zymogen granules. The integrated action of both these hormones provides for a heavy secretion of enzyme-rich pancreatic juice.

Liver

The liver is the second-largest organ of the body (the largest is the skin) and the largest gland, weighing about 1-1.5 kg. It is situated in the abdominal cavity beneath the diaphragm. The liver is the organ in which nutrients absorbed in the digestive tract are processed and stored for use by other parts of the body. It is thus an interface between the digestive system and the blood. Most of its blood (70-80%) comes from the portal vein, arising from the stomach, intestines, and spleen; the smaller percentage (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 and for neutralizing and eliminating toxic substances. Elimination occurs in the bile, an exocrine secretion of the liver that is important for lipid digestion. The liver also has the very important function of producing plasma proteins, such as albumin, other carrier proteins, coagulation factors, and growth factors.

Stroma

The liver is covered by a thin connective tissue capsule (**Glisson's capsule**) 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 that supports the hepatocytes and sinusoidal endothelial cells of the liver lobules is formed.

The Liver Lobule

The basic structural component of the liver is the liver cell, or **hepatocyte**. These epithelial cells are grouped in interconnected plates and constitute two-thirds of the mass of the liver. In light-microscope sections, structural units called **liver lobules** can be seen. The liver lobule is formed of a polygonal mass of tissue about 0.7 x 2 mm in size, with **portal spaces** at the periphery and a vein, called the **central or centrolobular vein,** in the center. Portal spaces, regions located in the corners of the lobules, contain connective tissue, bile ducts, lymphatics, nerves, and blood vessels. The human liver contains three to six portal spaces per lobule, each with a venule (a branch of the portal vein), an arteriole (a branch of the hepatic artery), a duct (part of the bile duct system), and lymphatic vessels. The venule contains blood coming from the superior and inferior mesenteric and splenic veins. The arteriole contains oxygen-rich blood coming from the celiac trunk of the abdominal aorta. The duct, lined by cuboidal epithelium, carries bile synthesized by the hepatocytes and eventually empties into the hepatic duct. One or more lymphatics carry lymph, which eventually enters the blood circulation. In certain animals (eg, pigs), the lobules are separated by a layer of connective tissue. This is not the case in humans, where the lobules are in close contact along most of their length, making it difficult to establish the exact limits between different lobules.

The hepatocytes in the liver lobule are radially disposed and are arranged like the bricks of a wall. These cellular plates are directed from the periphery of the lobule to its center and anastomose freely, forming a labyrinthine and spongelike structure. The space between these plates contains capillaries, the **liver sinusoids**. The Circulatory System, sinusoidal capillaries are irregularly dilated vessels composed solely of a discontinuous layer of fenestrated endothelial cells. The fenestrae are about 100 nm in diameter, have no diaphragm, and are grouped in clusters. There are also spaces between the endothelial cells, which, together with the cellular fenestrae and a discontinuous basal lamina (depending on the species), give these vessels great permeability.

A subendothelial space known as the **space of Disse** separates the endothelial cells from the hepatocytes. The fenestrae and discontinuity of the endothelium allow the free flow of plasma but not of cellular elements into the space of Disse, permitting an easy exchange of molecules (including macromolecules) from the sinusoidal lumen to the hepatocytes and vice versa. This exchange is physiologically important not only because of the large

number of macromolecules (eg, lipoproteins, albumin, fibrinogen) secreted into the blood by hepatocytes but also because the liver takes up and catabolizes many of these large molecules. The basolateral side of the hepatocyte, which lines the space of Disse, contains many microvilli and demonstrates endocytic and pinocytic activity. The sinusoid is surrounded and supported by a delicate sheath of reticular fibers. In addition to the endothelial cells, the sinusoids contain macrophages known as **Kupffer cells**. These cells are found on the luminal surface of the endothelial cells, within the sinusoids. Their main functions are to metabolize aged erythrocytes, digest hemoglobin, secrete proteins related to immunological processes, and destroy bacteria that eventually enter the portal blood through the large intestine. Kupffer cells account for 15% of the liver cell population. Most of them are located in the periportal region of the liver lobule, where they are very active in phagocytosis. In the space of Disse (perisinusoidal space), **fat-storing cells,** also called stellate or Ito's cells, contain vitamin and rich lipid inclusions. In the healthy liver, these cells have several functions, such as uptake, storage, and release of retinoids, synthesis and secretion of several extracellular matrix proteins and proteoglycans, secretion of growth factors and cytokines, and the regulation of the sinusoidal lumen diameter in response to different regulators (eg, prostaglandins, thromboxane A_2). Blood Supply

Portal Vein System

The portal vein branches repeatedly and sends small **portal venules** to the portal spaces. The portal venules branch into the **distributing veins** that run around the periphery of the lobule. From the distributing veins, small **inlet venules** empty into the **sinusoids.** The sinusoids run radially, converging in the center of the lobule to form the **central vein**. This vessel has thin walls consisting only of endothelial cells supported by a sparse population of collagen fibers. As the central vein progresses along the lobule, it receives more and more sinusoids and gradually increases in diameter. At its end, it leaves the lobule at its base by merging with the larger **sublobular vein**. The sublobular veins gradually converge and fuse, forming the two or more large **hepatic veins** that empty into the inferior vena cava.

Arterial System

The hepatic artery branches repeatedly and forms the **interlobular arteries.** Some of these arteries irrigate the structures of the portal spaces, and others form arterioles that end directly in the sinusoids at various distances from the portal spaces, thus providing a mixture of arterial and portal venous blood in the sinusoids. The main function of the arterial system is to supply an adequate amount of oxygen to hepatocytes.

Blood flows from the periphery to the center of the **liver lobule.** Consequently, oxygen and metabolites, as well as all other toxic or nontoxic substances absorbed in the intestines, reach the peripheral cells first and then reach the central cells of the lobule. This direction of blood flow partly explains why the behavior of the perilobular cells differs from that of the centrolobular cells. This duality of behavior of the hepatocyte is particularly evident in

pathological specimens, where changes are seen in either the central cells or the peripheral cells of the lobule.

The Hepatocyte

Hepatocytes are polyhedral, with six or more surfaces, and have a diameter of 20-30 m. In sections stained with hematoxylin and eosin (H&E), the cytoplasm of the hepatocyte is eosinophilic, mainly because of the large number of mitochondria and some smooth endoplasmic reticulum. Hepatocytes located at different distances from the portal spaces show differences in structural, histochemical, and biochemical characteristics. The surface of each hepatocyte is in contact with the wall of the sinusoids, through the space of Disse, and with the surfaces of other hepatocytes. *Wherever two hepatocytes abut, they delimit a tubular space between them known as the* **bile canaliculus**.

The canaliculi, the first portions of the bile duct system, are tubular spaces 1-2 m in diameter. They are limited only by the plasma membranes of two hepatocytes and have a small number of microvilli in their interiors. The cell membranes near these canaliculi are firmly joined by tight junctions. Gap junctions are frequent between hepatocytes and are sites of intercellular communication, an important process in the coordination of these cells' physiological activities. The bile canaliculi form a complex anastomosing network progressing along the plates of the liver 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. At the periphery, bile enters the **bile ductules,** or **Hering's canals**, composed of cuboidal cells. After a short distance, the 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.

The surface of the hepatocyte that faces the space of Disse contains many microvilli that protrude into that space, but there is always a space between them and the cells of the sinusoidal wall. The hepatocyte has one or two rounded nuclei with one or two nucleoli. Some of the nuclei are polyploid, ie, they contain some even multiples of the haploid number of chromosomes. Polyploid nuclei are characterized by their greater size, which is proportional to their ploidy. The hepatocyte has an abundant endoplasmic reticulumâ both smooth and rough. In the hepatocyte, the rough endoplasmic reticulum forms aggregates dispersed in the cytoplasm; these are often called **basophilic bodies.** Several proteins (eg, blood albumin, fibrinogen) are synthesized on polyribosomes in these structures. Various important processes take place in the smooth endoplasmic reticulum, which is distributed diffusely throughout the cytoplasm. This organelle is responsible for the processes of oxidation, methylation, and conjugation required for inactivation or detoxification of various substances before their excretion from the body. The smooth endoplasmic

reticulum is a labile system that reacts promptly to the molecules received by the hepatocyte.

The hepatocyte frequently contains glycogen. This polysaccharide appears in the electron microscope as coarse, electron-dense granules that frequently collect in the cytosol close to the smooth endoplasmic reticulum. The amount of glycogen present in the liver conforms to a diurnal rhythm; it also depends on the nutritional state of the individual. Liver glycogen is a depot for glucose and is mobilized if the blood glucose level falls below normal. In this way, hepatocytes maintain a steady level of blood glucose, one of the main sources of energy for use by the body.

Each hepatocyte has approximately 2000 mitochondria. Another common cellular component is the lipid droplet, whose numbers vary greatly. Hepatocyte lysosomes are important in the turnover and degradation of intracellular organelles. Like lysosomes, peroxisomes are enzyme-containing organelles abundant in hepatocytes. Some of their functions are the oxidation of excess fatty acids, breakdown of the hydrogen peroxide generated by this oxidation (by means of catalase activity), breakdown of excess purines (AMP, GMP) to uric acid, and participation in the synthesis of cholesterol, bile acids, and some lipids used to make myelin. Golgi complexes in the hepatocyte are also numerous up to 50 per cell. The functions of this organelle include the formation of lysosomes and the secretion of plasma proteins (eg, albumin, proteins of the complement system), glycoproteins (eg, transferrin), and lipoproteins (eg, very low-density lipoproteins).

Bile secretion is an exocrine function in the sense that hepatocytes promote the uptake, transformation, and excretion of blood components into the bile canaliculi. Bile has several other essential components in addition to water and electrolytes: bile acids, phospholipids, cholesterol, lecithin, and bilirubin. About 90% of these substances are derived by absorption from the distal intestinal epithelium and are transported by the hepatocyte from the blood to bile canaliculi (enterohepatic recirculation). About 10% of bile acids are synthesized in the smooth endoplasmic reticulum of the hepatocyte by conjugation of cholic acid (synthesized by the liver from cholesterol) with the amino acid glycine or taurine, producing glycocholic and taurocholic acids. Bile acids have an important function in emulsifying the lipids in the digestive tract, promoting easier digestion by lipases and subsequent absorption.

Lipids and carbohydrates are stored in the liver in the form of triglycerides and glycogen. This capacity to store metabolites is important, because it supplies the body with energy between meals. The liver also serves as the major storage compartment for vitamins, especially vitamin A. Vitamin A originates in the diet, reaching the liver along with other dietary lipids in the form of chylomicrons. In the liver, vitamin A is stored in Ito's cells.

The hepatocyte is also responsible for the synthesis of glucose from other metabolites such as lipids and amino acids by means of a complex enzymatic process called **gluconeogenesis**. It is also the main site of amino acid deamination, resulting in the

production of urea. Urea is transported through the blood to the kidney and is excreted by that organ.

Various drugs and substances can be inactivated by oxidation, methylation, or conjugation. The enzymes participating in these processes are located mainly in the smooth endoplasmic reticulum. Glucuronyltransferase, the enzyme that conjugates glucuronic acid to bilirubin, also causes conjugation of several other compounds such as steroids, barbiturates, antihistamines, and anticonvulsants. Under certain conditions, drugs that are inactivated in the liver can induce an increase in the hepatocyte's smooth endoplasmic reticulum, thus improving the detoxification capacity of the organ.

Biliary Tract

The daily basal secretion of bile is approximately 500 mL. The bile produced by the hepatocyte flows through the **bile canaliculi, bile ductules,** and **bile ducts.** These structures gradually merge, forming a network that converges to form the right and left hepatic ducts, which unite to form the common **hepatic duct.** The common hepatic duct, after receiving the **cystic duct** from the gallbladder, continues to the duodenum as the **common bile duct** (ductus choledochus).

The hepatic, cystic, and common bile ducts are lined with a mucous membrane of simple columnar epithelium. The lamina propria is thin and is surrounded by an inconspicuous layer of smooth muscle. This muscle layer becomes thicker near the duodenum and finally, in the intramural portion, forms a sphincter that regulates bile flow (sphincter of Oddi).

Gallbladder

The gallbladder is a hollow, pear-shaped organ attached to the lower surface of the liver. It can store 30-50 mL of bile. The wall of the gallbladder consists of a mucosa composed of simple columnar epithelium and lamina propria, a layer of smooth muscle, a perimuscular connective tissue layer, and a serous membrane.

The mucosa has abundant folds that are particularly evident when the gallbladder is empty. The epithelial cells are rich in mitochondria. All these cells are capable of secreting small amounts of mucus. Tubuloacinar mucous glands near the cystic duct are responsible for the production of most of the mucus present in bile. The main function of the gallbladder is to store bile, concentrate it by absorbing its water, and release it when necessary into the digestive tract. This process depends on an active sodium-transporting mechanism in the gallbladder's epithelium. Water absorption is an osmotic consequence of the sodium pump. Contraction of the smooth muscle of the gallbladder is induced by **cholecystokinin,** a hormone produced by enteroendocrine cells located in the epithelial lining of the small intestine. Release of cholecystokinin is, in turn, stimulated by the presence of dietary fats in the small intestine.