ORGANS ASSOCIATED WITH THE DIGESTIVE TRACT: INTRODUCTION

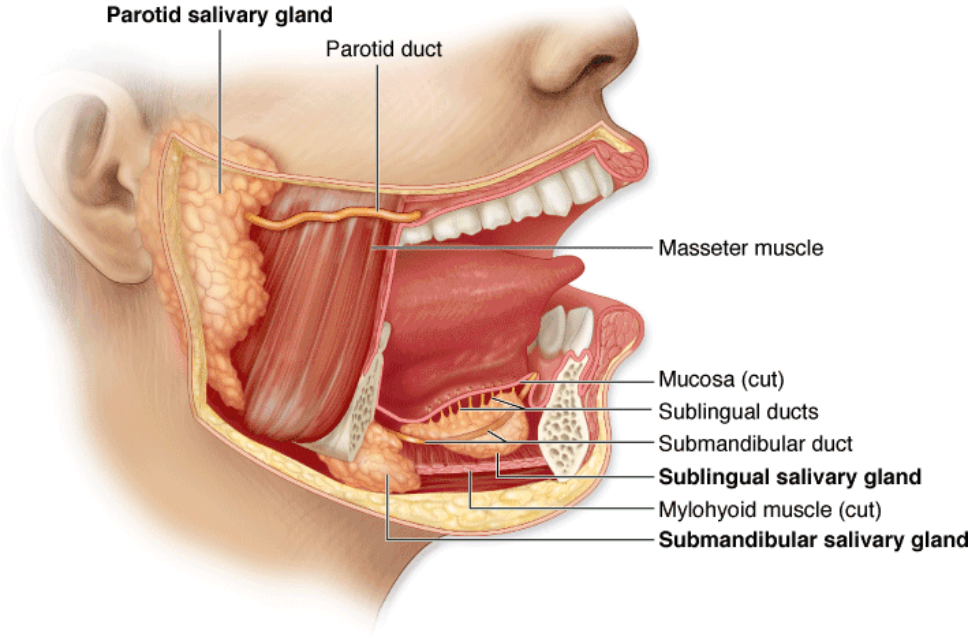
The organs associated with the digestive tract include the salivary glands, the pancreas, the liver, and the gallbladder. Products of these organs facilitate transport and digestion of food within the gastrointestinal tract. The main functions of the salivary glands are to wet and lubricate ingested 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** (Figure 16–1), in addition to minor glands in mucosa and submucosa throughout the oral cavity which secrete 10% of the total volume of saliva.

Figure 16–1.



Major salivary glands.

About 90% of saliva is produced by three bilateral pairs of salivary glands: the parotid, submandibular, and sublingual glands. Locations and relative sizes of these glands are shown here diagrammatically. These glands plus microscopic salivary glands throughout the oral mucosa produce 0.75 to 1.50 L of saliva daily.

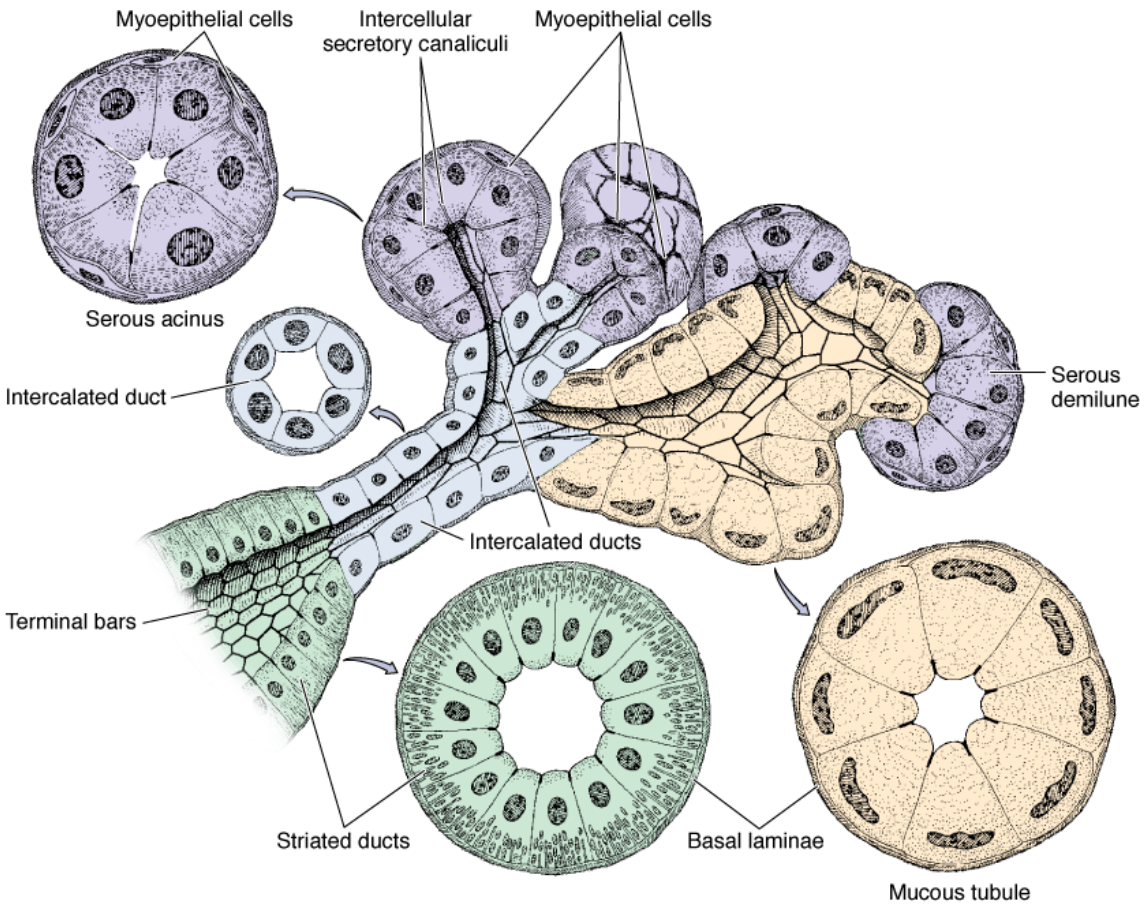
MEDICAL APPLICATION

Reduced function of the major salivary glands due to diseases or radiotherapy is associated with caries, atrophy of the oral mucosa and speech difficulties.

A capsule of connective tissue surrounds each major salivary gland. The parenchyma of each consists of secretory endpieces and a branching duct system arranged in **lobules**, separated by connective tissue septa originating from the capsule. The secretion of each gland is either serous, seromucous, or mucous, depending on its glycoprotein mucin content. Saliva from the parotids is serous and watery. The submandibular and sublingual glands produce a seromucous secretion, with mostly mucus from the minor glands. Saliva is modified by the cells of the duct system draining the secretory units, with much Na^+ and Cl^- reabsorbed while certain growth factors and digestive enzymes are added.

Two major kinds of secretory cells occur, arranged in separate units. **Serous cells** are polarized protein-secreting cells, usually pyramidal in shape, with a broad base resting on the basal lamina and a narrow apical surface facing the lumen (Figures 16–2 and 16-3). Adjacent cells are joined together by junctional complexes and usually form a spherical mass of cells called an **acinus,** with a very small lumen in the center (Figure 16–2). Acini and their duct system resemble grapes attached to a stem. Serous acinar cells largely produce digestive enzymes and other proteins.

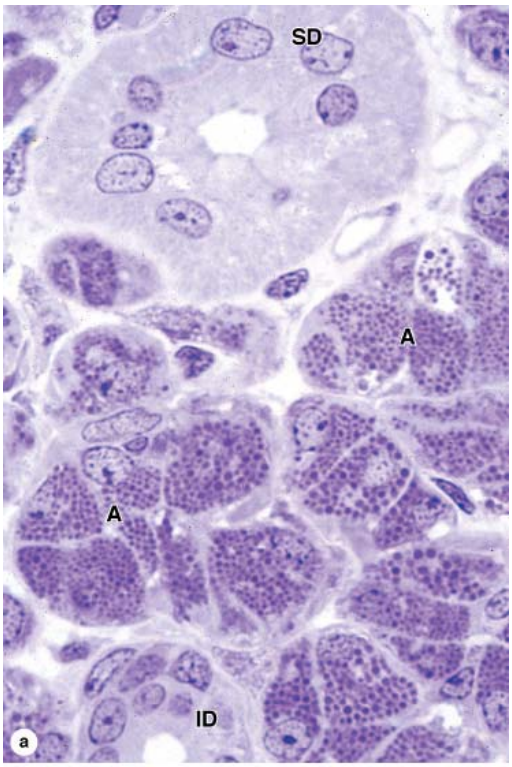
Figure 16–2.

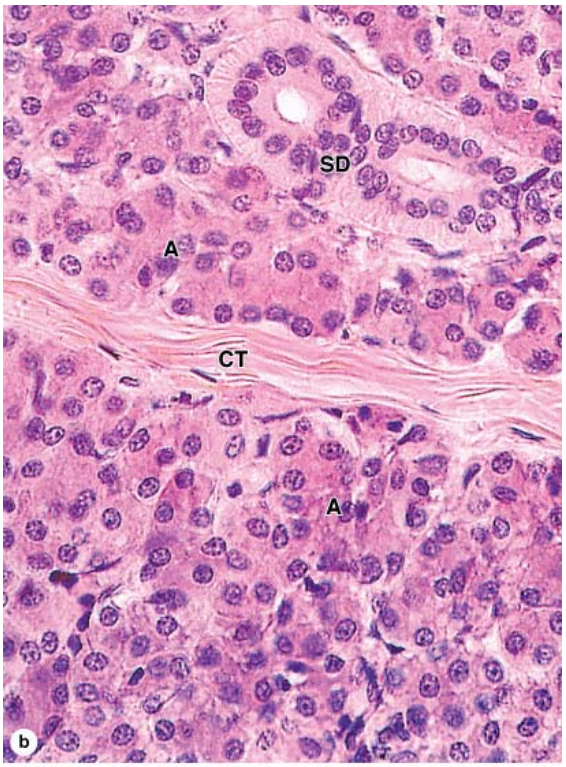


Epithelial components of a submandibular gland lobule.

The secretory portions are composed of pyramidal serous (light blue) and mucous (light brown) cells. Serous cells are typical protein-secreting cells, with rounded nuclei, accumulation of rough ER in the basal third, and an apex filled with protein-rich secretory granules. The nuclei of mucous cells, flattened with condensed chromatin, are located near the bases of the cells. The short intercalated ducts are lined with cuboidal epithelium. The striated ducts are composed of columnar cells with characteristics of ion-transporting cells: basal membrane invaginations with mitochondrial accumulations. Myoepithelial cells are shown in the serous acini.

Figure 16–3.



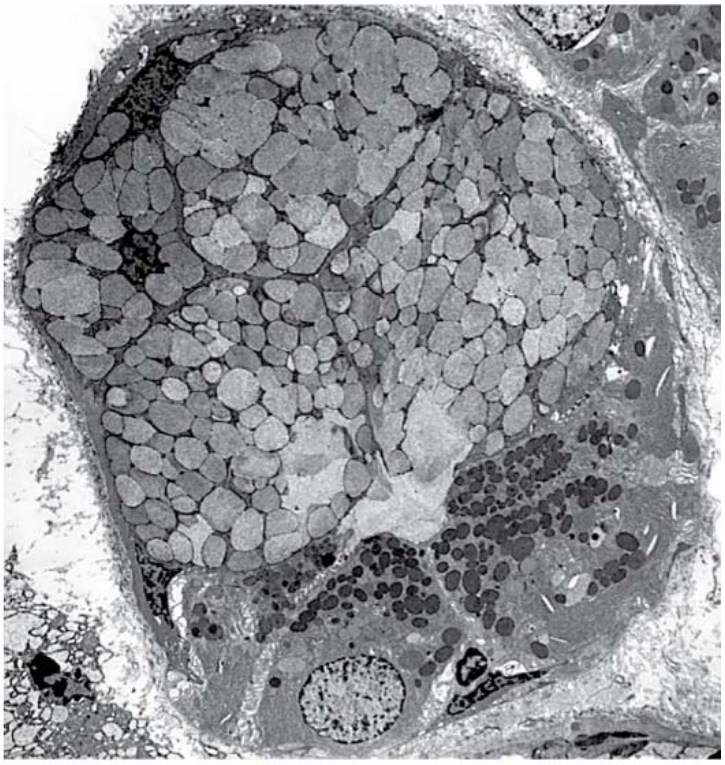


Parotid gland.

The large parotid gland consists entirely of serous acini with cells producing amylase and other proteins for storage in secretory granules**. (a):** Micrograph of a parotid gland shows densely packed serous acini (A) with ducts. Secretory granules of serous cells are clearly shown in this plastic section, as well as both an intercalated duct (ID) and striated duct (SD), both cut transversely. X400. PT. **(b):** Striations of a duct (SD) are better seen here, along with a septum (CT) and numerous serous acini (A). The connective tissue often includes adipocytes. X200. H&E.

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 (Figures 16–3 and 16–4), 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.

Figure 16–4.



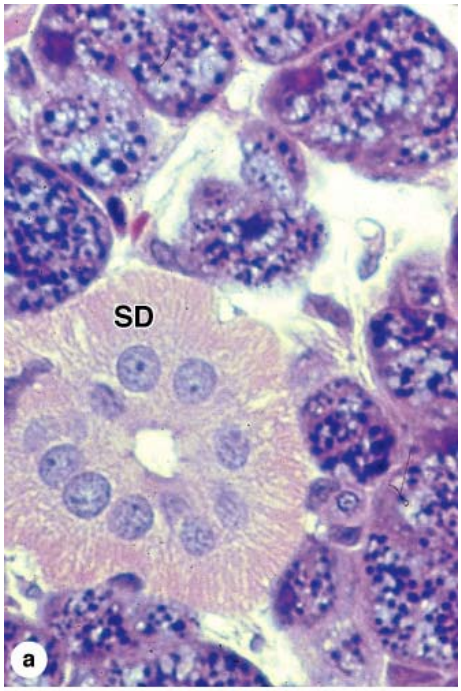
Ultrastructure of serous and mucous cells.

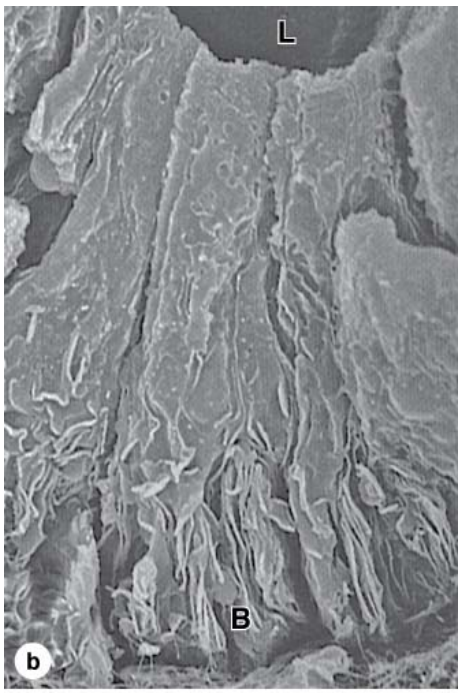
A micrograph of a mixed acinus from a submandibular gland shows both serous and mucous cells. Mucous cells (upper area shown here) have large, hydrophilic granules like those of goblet cells. Serous cells (lower area) have small, dense granules that stain more intensely with most stains. X2500. (With permission, from John D. Harrison, Department of Oral Pathology, King's College, London.)

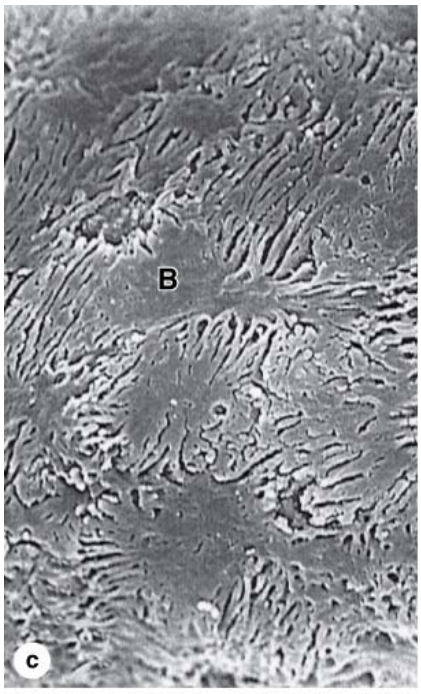
Myoepithelial cells, described in Chapter 4, are found inside the basal lamina of the secretory units and (to a lesser extent) the initial part of the duct system (Figure 16–2). Surrounding the secretory portion myoepithelial cells are well developed and branched (and are sometimes called basket cells), 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** (Figure 16–2). 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 (Figure 16–5). 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.

Figure 16–5.







Striated ducts.

(a): This light micrograph of a striated duct (SD) shows very faint pink striations in the basal half of the columnar cells. The striations are produced by mitochondria located in the folds of the lateral cell membrane. X200. H&E. **(b):** SEM indicates that the apical ends of the cells are joined together near the small lumen (L), with interdigitating folds of cell membrane best developed at the basal end (B). X4000. **(c):** This SEM shows the bases (B) of several such cells with the basal lamina removed, revealing the extensive interlocking of folded membrane between neighboring cells. Mitochondria between the folds supply energy for membrane ion pumps and ion uptake from saliva is rapid and efficient. X4000

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.

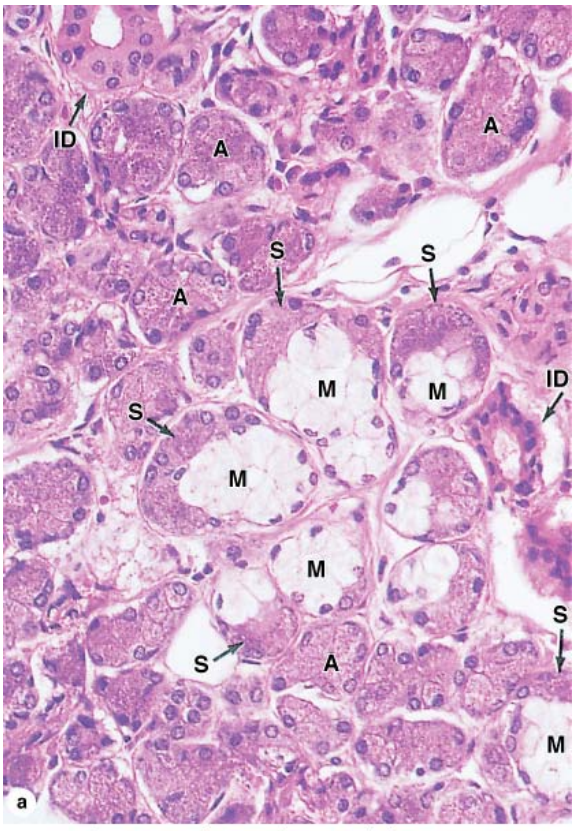
The striated ducts of each lobule converge and drain into ducts located in the connective tissue septa separating lobules, where they become **interlobular,** or **excretory, ducts.** They are initially lined with pseudostratified or stratified cuboidal epithelium, but more distal parts of the excretory 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.

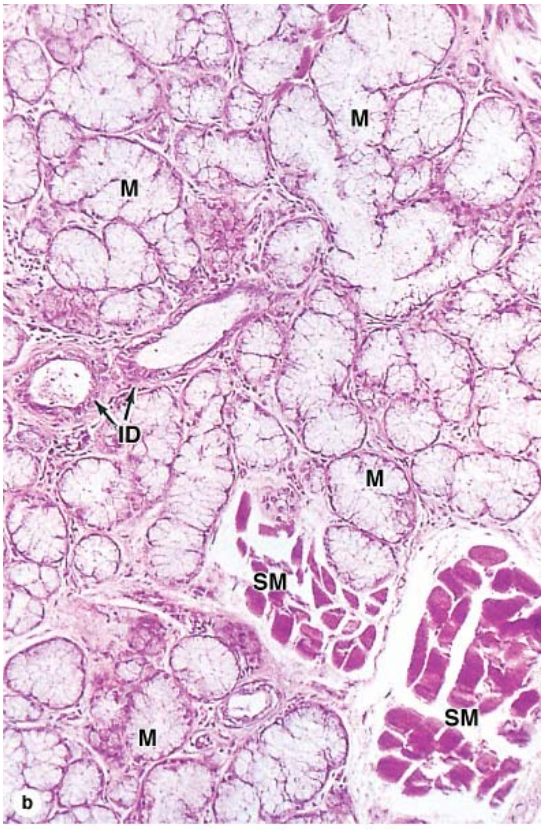
Vessels and nerves enter the large salivary glands at a hilum and gradually branch into the lobules. A rich vascular and nerve plexus surrounds the secretory and ductal components of each lobule. The capillaries surrounding the secretory endpieces are very important for the secretion of saliva, which 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 (Figure 16–3). Serous cells contain secretory granules with abundant **α-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 (Figures 16–4 and 16–6), with secretory portions containing 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. 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** (Figure 16–6a). Lateral and basal membrane infoldings of the serous cells increase the ion-transporting surface area and facilitate electrolyte and water transport. In addition to α-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 (Figure 16–6b), 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.

Figure 16–6.





Submandibular gland and sublingual gland.

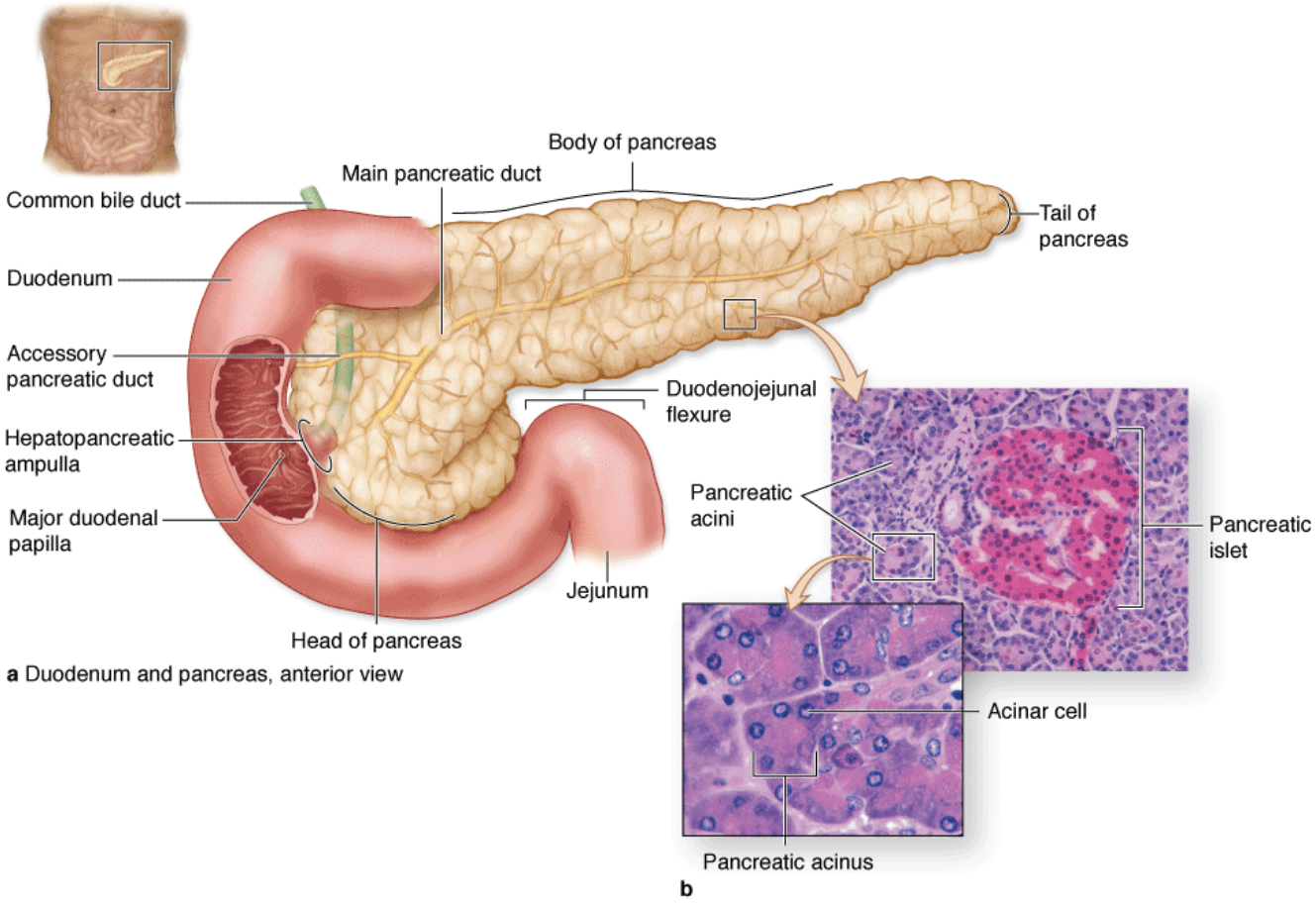
(a): Submandibular gland is a mixed serous and mucous gland (serous cells predominate) and shows well-stained cells in serous acini (A) and in serous demilunes (S) and pale-staining mucous cells (M) grouped as tubules in this tubuloacinar gland. Small intralobular ducts (ID) drain each lobule, but these are not composed of columnar cells with well-developed striations. X340. H&E. **(b):** Sublingual gland is a mixed but largely mucous gland with a tubuloacinar arrangement of poorly stained mucous cells (M). Small intralobular ducts (ID) are seen in connective tissue, as well as small fascicles of lingual striated muscle (SM). X140. H&E.

Small, nonencapsulated salivary glands are distributed throughout the oral mucosa and submucosa with short ducts to the oral cavity. Minor salivary glands are usually mucous, an exception being the small serous glands at the bases of circumvallate papillae on the back of the tongue (Chapter 15). B lymphocytes releasing IgA are common within the minor salivary glands.

PANCREAS

The pancreas is a mixed exocrine-endocrine gland that produces both digestive enzymes and hormones (Figures 16–7 and 16–8). 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.

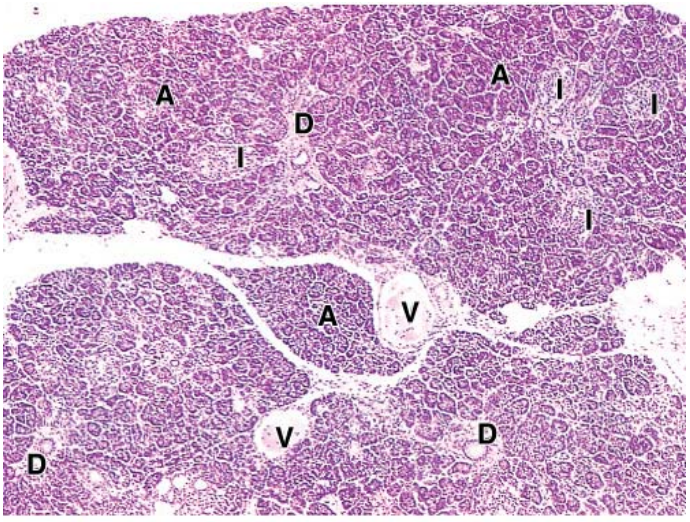
Figure 16–7.



Pancreas and duodenum.

(a): The main regions of the pancreas are shown in relation to the two pancreatic ducts and the duodenum. **(b):** Micrographs show a pancreatic islet and several pancreatic acini. X75 and X200. H&E.

Figure 16–8.



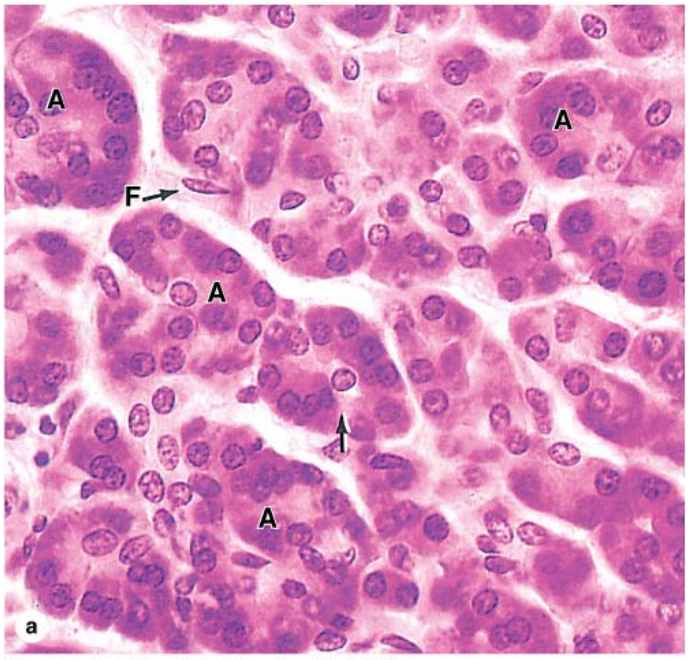
Pancreas.

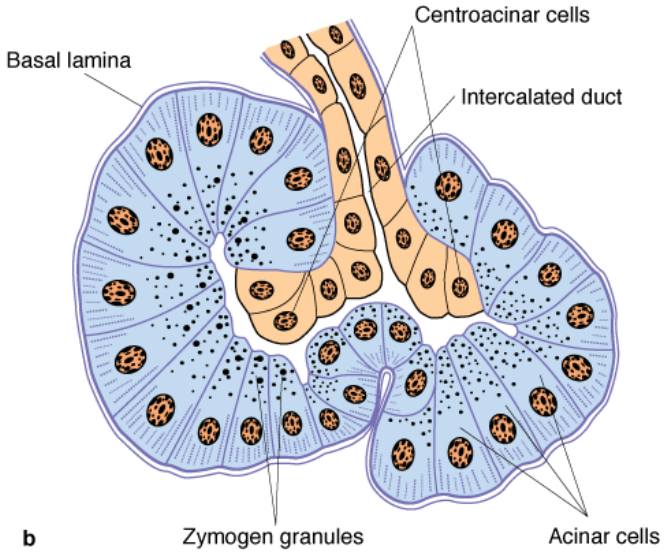
Low power view of pancreas includes several islets (I) surrounded by many serous acini (A). The larger interlobular ducts (D) are lined by simple columnar epithelium. The ducts and blood vessels (V) are located in connective tissue, which also provides a thin capsule to the entire gland and thin septa separating the lobules of

secretory acini. X20. H&E.

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) (see Chapter 20). 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 (Figure 16–9). 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.

Figure 16–9.



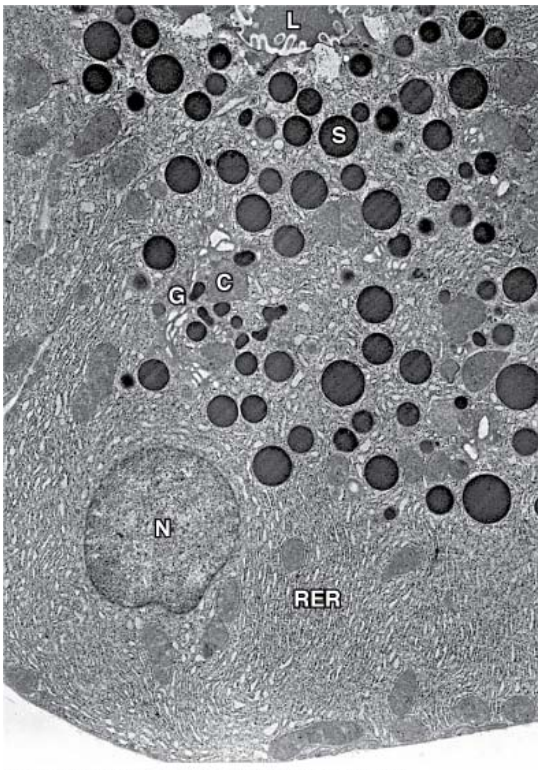


Pancreatic acini.

(a): Micrograph of exocrine pancreas shows the serous, enzyme-producing cells arranged in small acini (A) with very small lumens. Acini are surrounded by small amounts of connective tissue with fibroblasts (F). Each acinus is drained by an intercalated duct with its initial cells, the centroacinar cells (arrow), inserted into the acinar lumen. X200. H&E. **(b):** The diagram shows the arrangement of cells more clearly. Under the influence of secretin, the centroacinar and other cells of these small ducts secrete a copious HCO_3^- - rich fluid that hydrates and alkalinizes the enzymatic secretions of the acinar cells. Pancreatic acini lack myoepithelial cells and their intercalated ducts lack striations.

Each exocrine acinus of the pancreas is composed of several serous cells surrounding a very small lumen (Figure 16–9). The acinar cells are highly polarized, with a spherical nucleus, and are typical protein-secreting cells (Figure 16–10). The number of zymogen granules present in each cell varies and is maximal in animals that have fasted.

Figure 16–10.



Pancreatic acinar cells.

TEM of a pancreatic acinar cell shows its pyramidal shape and the round, basal nucleus (N) surrounded by cytoplasm packed with cisternae of rough ER (RER). The Golgi apparatus (G) is situated at the apical side of the nucleus and is associated with condensing vacuoles (C) and numerous secretory (zymogen) granules (S). The small lumen (L) of the acinus contains proteins recently released from the cell by exocytosis. Exocytosis of digestive enzymes from secretory granules is promoted by CCK, released from the duodenum when food enters that region from the stomach. X8000.

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**), **α-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.

MEDICAL APPLICATION

In acute necrotizing **pancreatitis**, the proenzymes may be activated and digest pancreatic tissues, leading to very serious complications. Possible causes include infection, gallstones, alcoholism, drugs, and trauma.

Pancreatic secretion is controlled mainly through two polypeptide hormones—**secretin** and **cholecystokinin (CCK)—**produced by enteroendocrine cells of the intestinal mucosa (duodenum and jejunum). The vagus (parasympathetic) nerve also stimulates pancreatic secretion and the autonomic system works in concert with the hormones to control pancreatic secretion.

Acid and partially digested food in the gastric **chyme** enters the duodenum and stimulates local release of CCK and secretin. CCK promotes the exocytosis of zymogens and enzymes from the pancreatic acinar cells. Secretin causes acinar and duct cells to add water and bicarbonate ions to the secreted proteins, producing an abundant alkaline fluid with its enzymes diluted but rich in electrolytic ions. This fluid neutralizes the acidic chyme and allows the pancreatic enzymes to function at their optimal pH range. The coordinated action of both hormones provides for proper secretion of enzyme-rich, alkaline pancreatic juice.

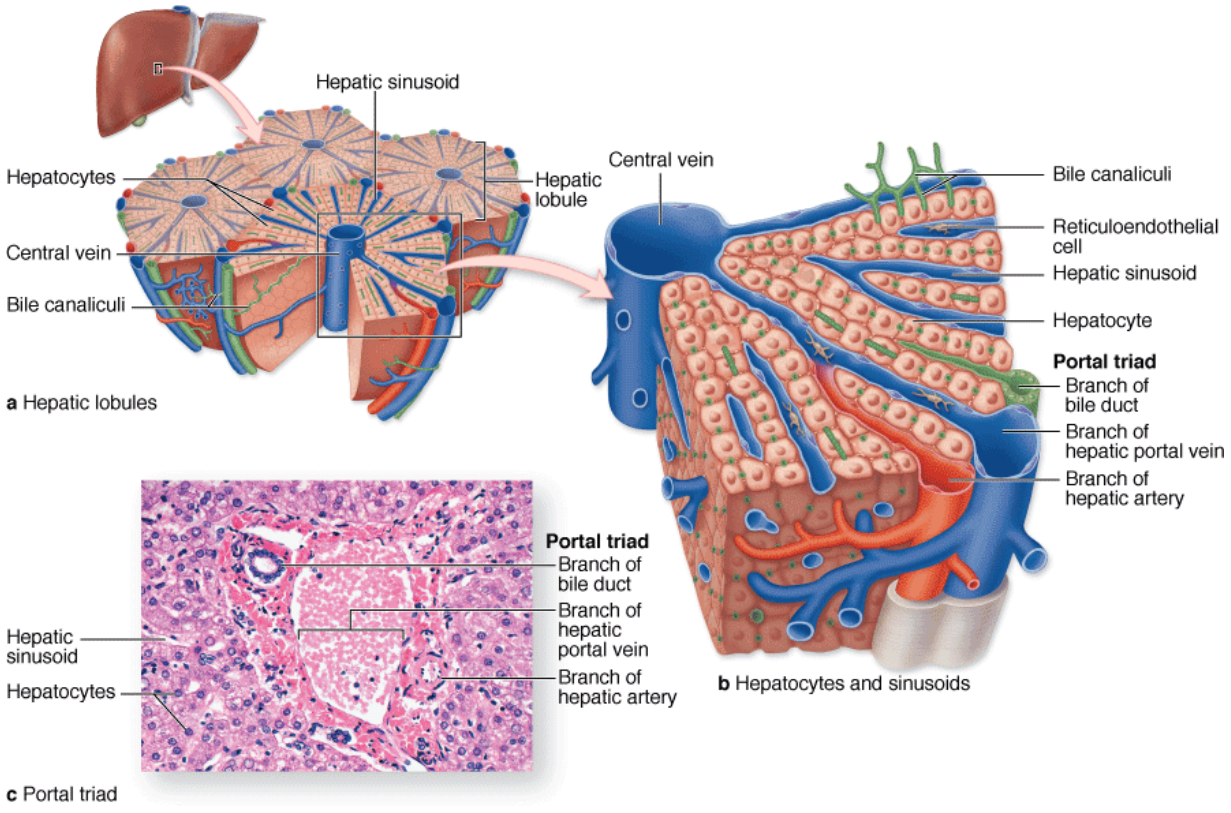
MEDICAL APPLICATION

In conditions of extreme malnutrition such as **kwashiorkor**, pancreatic acinar cells and other active protein-secreting cells atrophy and lose much of their rough ER, hindering production of digestive enzymes.

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 (Figure 16–11). 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.

Figure 16–11.



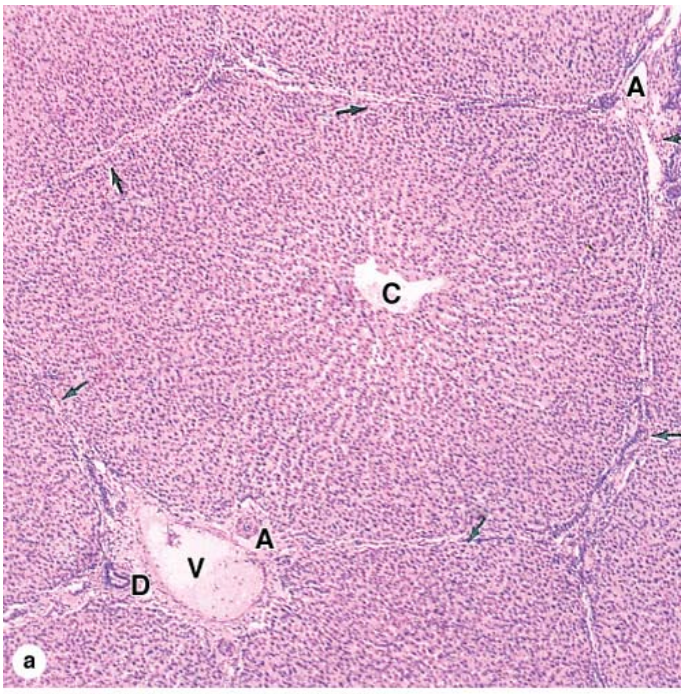
Liver.

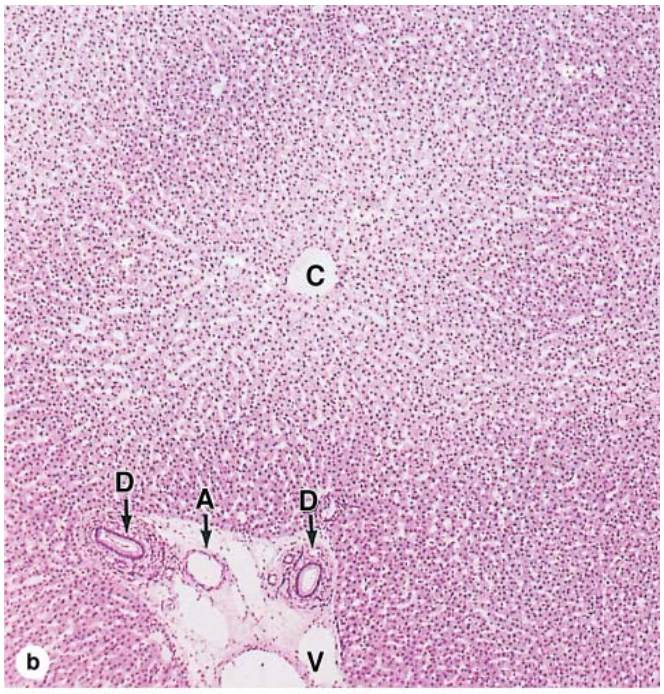
A large organ in the upper right quadrant of the abdomen, immediately below the diaphragm, the liver is composed of thousands of polygonal structures called hepatic lobules, which are the basic functional units of the organ. **(a):** Diagram shows a small central vein projecting through the center of each hepatic lobule and several sets of blood vessels defining the periphery. The peripheral vessels are grouped primarily in connective tissue comprising the portal tracts, which usually include a branch of the portal vein and a branch of the hepatic artery, as well as a branch of the bile duct. These comprise the portal triad. **(b):** Both blood vessels to each lobule give off sinusoids, which run between plates of hepatocytes and drain into the central vein. **(c):** Micrograph showing components of the portal triad. X220. H&E.

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 (Figures 16–12 and 16–13).

Figure 16–12.

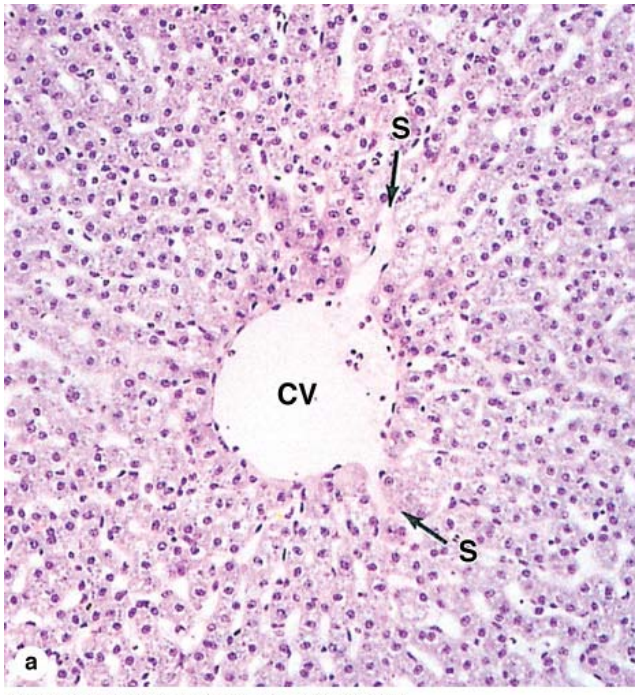


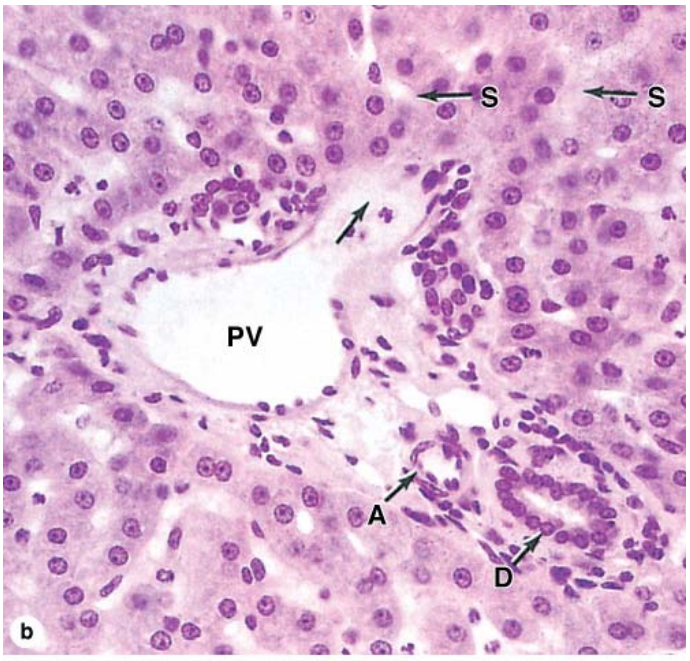


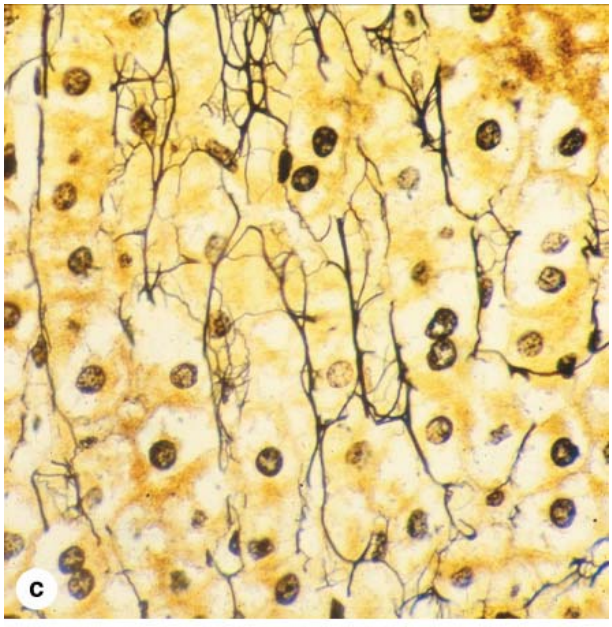
Hepatic lobule.

Cut transversely hepatic lobules are polygonal units showing plates of epithelial cells called hepatocytes radiating from a central venule (C). **(a):** Hepatic lobule of some mammals, such as the pig, are delimited on all sides by connective tissue. **(b):** Hepatic units of humans have much less connective tissue and their boundaries are more difficult to distinguish. In all cases peripheral connective tissue of portal areas with microvasculature and small bile duct (D) branches can be seen and in humans as in other mammals these are present at the boundaries between two or more hepatic lobules. The vessels near the bile ducts branches are a venule (V) off the portal vein and an arteriole (A) off the hepatic artery. Both X150. H&E.

Figure 16–13.







Hepatic lobule microvasculature.

(a): The hepatic lobule's central vein (CV) is actually a venule consisting of little more than an endothelial tube with smaller sinusoids (S) coming in from all directions. X200. H&E. **(b):** Peripheral portal areas contain more connective tissue and are the sites of the portal triad: a portal venule (PV), an arteriole (A) branching off the hepatic artery, and one or two branches of the bile duct (D). Blood flows (arrow) from these arterioles and venules into the sinusoids between the plates of hepatocytes that run to the central venule. In the portal area the bile ductules are lined by simple cuboidal epithelium. X400. H&E. **(c):** Reticulin (collagen type III) fibers running along the plates of hepatocytes are the major support for the sinusoids and central venules. Most connective tissue in the liver is found in the septa and portal tracts. X400. Silver.

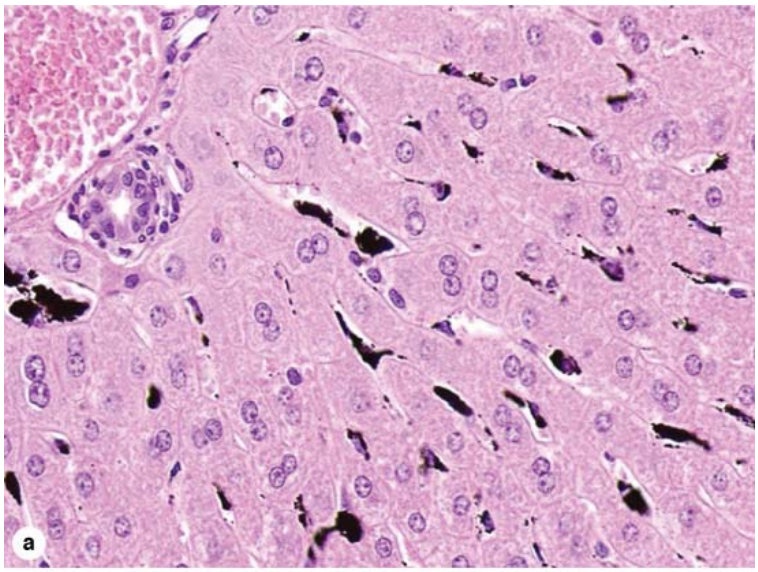
Hepatic Lobules

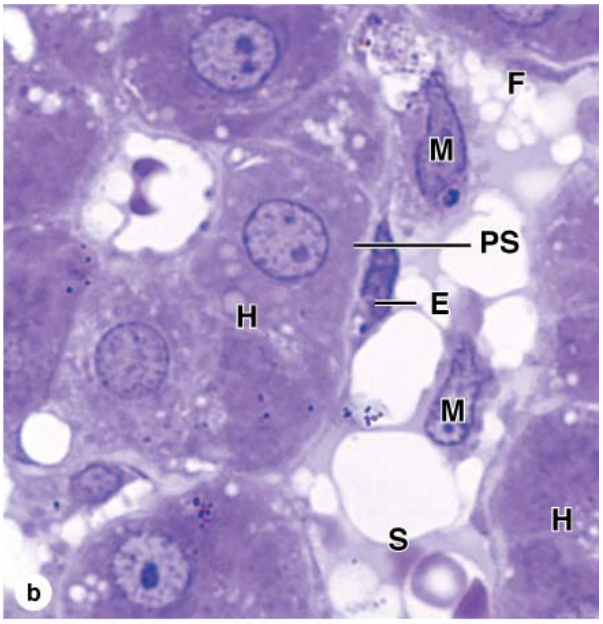
Liver cells or **hepatocytes** (Gr. *hepar,* liver, + *kytos,* cell) are epithelial cells grouped in interconnected plates. Hepatocytes are arranged into thousands of small (~0.7 x 2 mm), polyhedral **hepatic lobules** which are the classic structural and functional units of the liver (Figure 16–11). Each lobule has three to six **portal areas** at its periphery and a venule called a **central vein** in its center (Figures 16–11, 16–12, and 16–13). 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** (Figure 16–12). 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 (Figure 16–12).

Hepatocytes make up each of the interconnected plates like the bricks of a wall and the plates are arranged radially around the central vein (Figure 16–11). From the periphery of the lobule to its center, the plates of hepatocytes branch and anastomose freely, forming a rather sponge-like structure (Figure 16–12). The spaces between these plates contain important microvascular components, the **liver sinusoids** (Figures 16–11, 16–12, and 16–13). These irregularly dilated sinusoids consist only of a discontinuous layer of fenestrated endothelial cells (Figures 16–14 and 16–15). 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 (Figure 16–14). 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.

Figure 16–14.



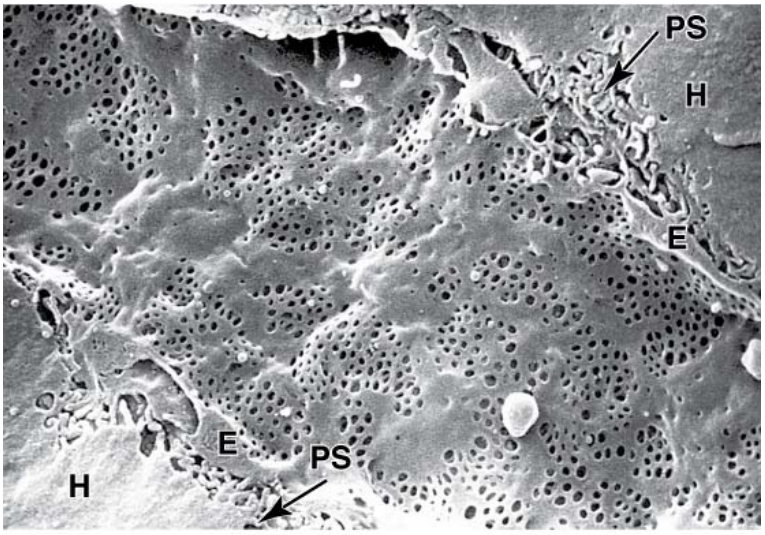


Hepatic sinusoids.

Nutrient-rich blood from the portal vein and oxygen-rich blood from the arteriole mix in the sinusoids running between the plates of hepatocytes from the portal areas to the central venules. Molecules in the blood are processed mainly by the hepatocytes, but other cells in or near the sinusoids are also important. Specialized stellate macrophages, often called Kupffer cells, are bound to the endothelial lumen of the sinusoids, where they detect and phagocytose effete erythrocytes. **(a):** Stellate macrophages are seen as black cells in a liver lobule from a rat injected with particulate India ink. X200. H&E.

(b): In this plastic section, stellate macrophages (M) are seen in the sinusoid (S) between two groups of hepatocytes (H). They are larger than the flattened endothelial cells (E). Between the endothelium and the hepatocytes is a thin space called the perisinusoidal space (PS), in which are located fibroblastic fat-storing cells (F), or Ito cells, that maintain the very sparse ECM of this compartment and are also specialized for vitamin A storage in small lipid droplets. These cells are numerous but are difficult to demonstrate in routine histological preparations. If their lipid droplets become very large or abundant, the fat-storing cells resemble adipocytes. X750. PT.

Figure 16–15.



Ultrastructure of the sinusoid wall.

SEM of the luminal surface of the endothelium lining a sinusoid in liver shows grouped fenestrations. At the border are seen cut edges of the endothelial cell (E) in this discontinuous sinusoid and hepatocytes (H). Between these two cells is the thin perisinusoidal space (PS), into which project microvilli from the hepatocytes surface. Blood plasma passes freely through the fenestrations into the perisinusoidal space, where the voluminous membrane of hepatocytes acts to remove many high and low molecular weight blood components and nutrients for storage and processing. Proteins synthesized and secreted from hepatocytes, such as albumin, fibrinogen, and other blood proteins, are released into the perisinusoidal space. X6500. (With permission, from Eddie Wisse, Electron Microscopy Unit, Department of Pathology, University of Maastricht, The Netherlands.)

Liver sinusoids are surrounded and supported by delicate sheathes of reticular fibers (Figure 16–13). 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 (Figure 16–14). 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 (Figure 16–14). 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.

MEDICAL APPLICATION

In chronically diseased liver, Ito cells proliferate and acquire the features of myofibroblasts, with or without the lipid droplets. Under these conditions, these cells are found close to the damaged hepatocytes and play a major role in the development of fibrosis, including the fibrosis secondary to **alcoholic liver disease**.

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** (Figure 16–11).

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** (Figures 16–11, 16-12, and 16–13). This vessel, like the sinusoids, has very thin walls consisting only of endothelial cells supported by a sparse population of collagen fibers (Figure 16–13). Central venules from each lobule converge into veins, which eventually form two or more large **hepatic veins** that empty into the inferior vena cava.

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

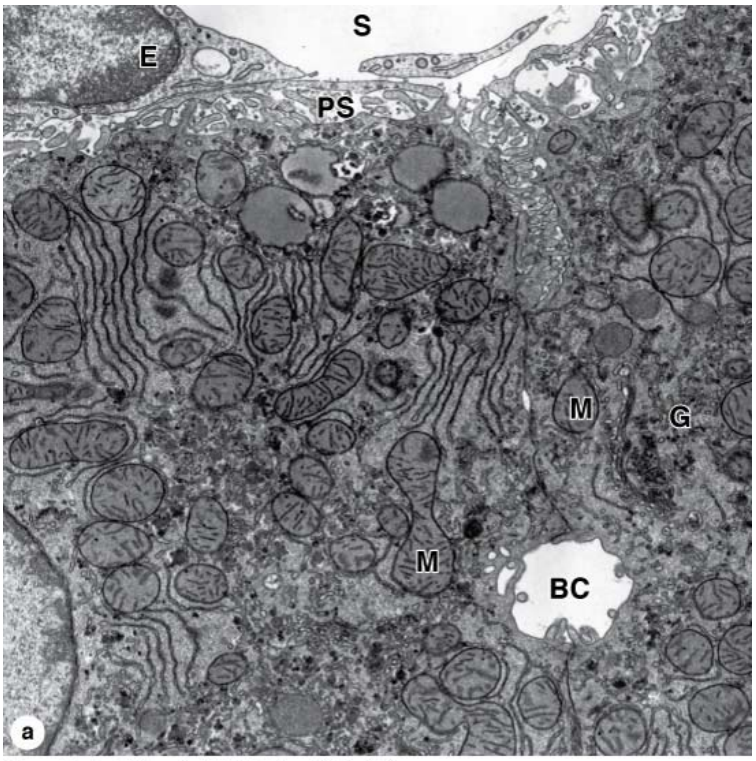
Blood always flows from the periphery to the center of each hepatic lobule. Consequently, oxygen and metabolites, as well as all other toxic or nontoxic substances absorbed in the intestines, reach the lobule's peripheral cells first and then the more central cells. This direction of blood flow partly 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.

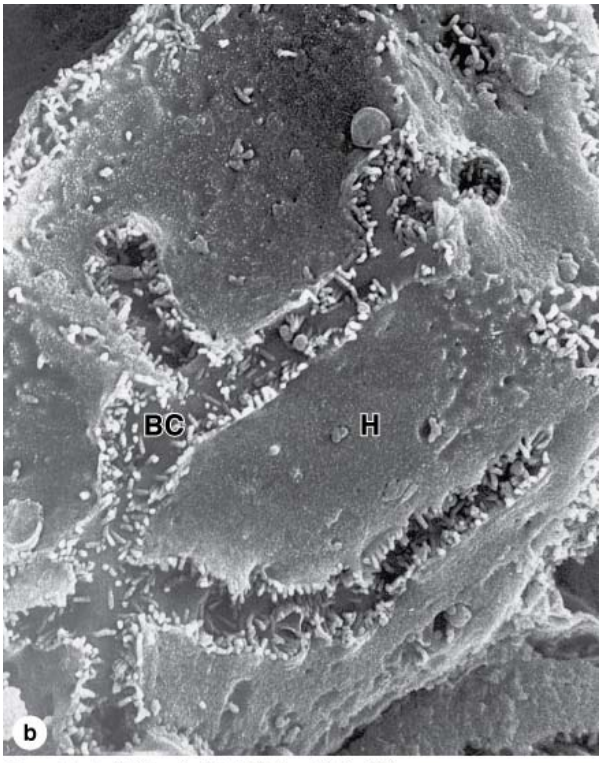
The Hepatocyte

Hepatocytes are large polyhedral cells, with six or more surfaces, and typical diameters of 20–30 μm. 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 (Figure 16–16). Where two hepatocytes abut, they delimit a tubular space between them known as the **bile canaliculus** (Figure 16–16).

Figure 16–16.





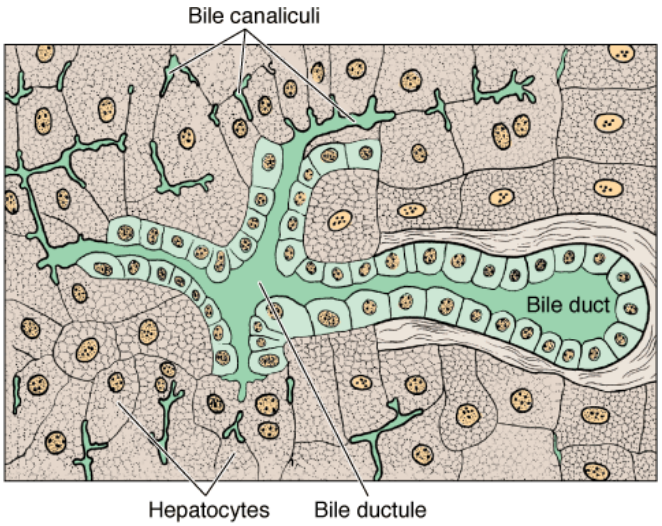
Ultrastructure of hepatocytes and bile canaliculi.

(a): TEM of hepatocytes show small bile canaliculi (BC) between two cells, with junctional complexes binding the cells firmly and tightly at these sites. The bile canaliculus is the site of exocrine secretion by hepatocytes. The two adjoining hepatocytes extend short microvilli and secrete bile components into this space. The hepatocytes have many mitochondria (M), small electron-dense glycogen granules, and Golgi complexes (G) and extend more numerous microvilli into the perisinusoidal space (PS), which is the site where hepatocytes remove and add components in plasma. The endothelial cell (E) lining the sinusoid (S) is also seen. X9500. **(b):** SEM of hepatocytes (H) broken apart from one another reveals the length of a bile canaliculus (BC) along the cell's surface. Such canaliculi run between the cells of the hepatocyte plates in the hepatic lobules and carry bile toward the portal areas where the canaliculi join cuboidal bile ductules. (Figure 16–16a, with permission, from Douglas L. Schmucker, Department of Anatomy, University of California, San Francisco.)

The canaliculi, the first portions of the bile duct system, are long spaces 1–2 μm in diameter. They are limited only by the plasma membranes of two hepatocytes, which extend a small number of microvilli into their interiors (Figure 16–16). 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 (Figure 16–11). 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** (Figure 16–17) composed of cuboidal epithelial cells called **cholangiocytes** (Figures 16–18 and 16–19). 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.

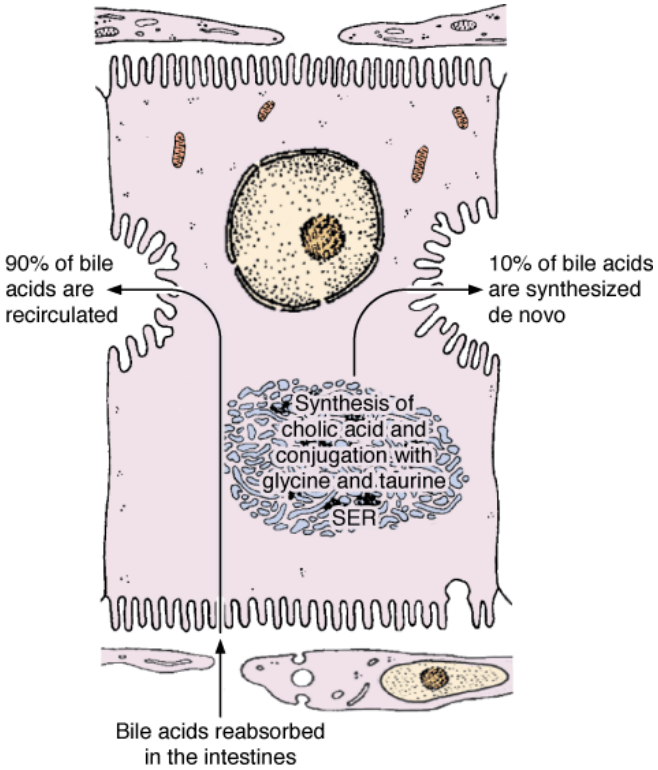
Figure 16–17.



Bile ductules.

Near the periphery of hepatic lobules, the bile canaliculi join with bile ductules lined by cuboidal epithelial cells called cholangiocytes. The ductules soon merge with branches of the bile ducts in the portal spaces. The branches merge from all over the liver and give rise to the left and right hepatic ducts which leave the organ at the hilum.

Figure 16–18.



Secretion of bile acids.

Bile acids are organic molecules, primarily cholic acid and its derivatives, found in bile excreted from hepatocytes into the system of bile canaliculi and ducts. These compounds are often deprotonated, becoming the bile salts. Stored in the gall bladder and released into the duodenum after a meal, bile acids emulsify fats, facilitating lipid breakdown and absorption. About 90% of bile acids are absorbed from the 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 ER of hepatocytes by conjugation of cholic acid (synthesized in hepatocytes from cholesterol) with the amino acid glycine or taurine, producing glycocholic and taurocholic acids.

Figure 16–19.