Secretin promotes water and HCO$_3^-$ secretion by the duct cells.

Autonomic (parasympathetic) nerve fibers also stimulate secretion from both acinar and duct cells.

**MEDICAL APPLICATION**

In the normal liver most dense connective tissue is found only in the portal areas, surrounding the blood vessels and bile ductule. In liver cirrhosis, which occurs late in chronic liver disease, fibrosis and proliferation of fibroblasts and hepatic stellate cells occur beyond the portal areas. The excessive connective tissue may disrupt the normal hepatic architecture and interfere with liver function.

**LIVER**

The liver is the largest internal organ, in adults averaging about 1.5 kg or 2% of the body weight. Located in the right upper quadrant of the abdomen just below the diaphragm (see Figure 15–1), the liver has major left and right lobes with two smaller inferior lobes, most of which are covered by a thin capsule and mesothelium of the visceral peritoneum. The capsule thickens at the hilum (or porta hepatis) on the inferior side, where the dual blood supply from the hepatic portal vein and hepatic artery enters the organ and where the hepatic vein, lymphatics, and common hepatic (bile) duct exit.

The main digestive function of the liver is production of bile, a complex substance required for the emulsification, hydrolysis, and uptake of fats in the duodenum. The liver is also the major interface between the digestive system and the blood, as the organ in which nutrients absorbed in the small
Low-power view of pancreas includes several islets (I) surrounded by many serous acini (A). The larger intralobular 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.

(a) Micrograph of exocrine pancreas shows the serous, enzyme-producing cells arranged in small acini (A) with very small lumens. Acini are surrounded by only 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 intercalated duct cells secrete a copious HCO₃⁻-rich fluid that hydrates, flushes, and alkalinizes the enzymatic secretion of the acini.
intestine are processed before distribution throughout the body. About 75% of the blood entering the liver is nutrient-rich (but O$_2$-poor) blood from the portal vein arising from the stomach, intestines, and spleen; the other 25% comes from the hepatic artery and supplies the organ’s O$_2$.

**Hepatocytes** (Gr. hepar, liver), the key cells of this organ, are among the most functionally diverse cells of the body. In addition to an exocrine function in the secretion of bile components, hepatocytes and other liver cells process the contents of blood, with many specific functions:

- Synthesis and endocrine secretion into the blood of the major **plasma proteins**, including albumins, fibrinogen, apolipoproteins, transferrin, and many others
- Conversion of amino acids into glucose (**gluconeogenesis**)
- Breakdown (**detoxification** and conjugation of ingested toxins, including many drugs
- Amino acid **deamination**, producing **urea** removed from blood in kidneys
- **Storage of glucose** in glycogen granules and **triglycerides** in small lipid droplets

**FIGURE 16–10** Pancreatic acinar cell ultrastructure.

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 located at the apical side of the nucleus and associated with condensing vacuoles (C) and numerous secretory granules (S) with zymogen. 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 by enteroendocrine cells of the duodenum when food enters that region from the stomach. X8000.
Storage of vitamin A (in hepatic stellate cells) and other fat-soluble vitamins
- Removal of effete erythrocytes (by specialized macrophages, or Kupffer cells)
- Storage of iron in complexes with the protein ferritin

Hepatocytes & Hepatic Lobules

The liver’s unique histologic organization and microvasculature allow hepatocytes to perform their diverse metabolic, exocrine, and endocrine functions. Hepatocytes are large cuboidal or polyhedral epithelial cells, with large, round central nuclei and eosinophilic cytoplasm rich in mitochondria. The cells are frequently binucleated and about 50% of them are polyploid, with two to eight times the normal chromosome number.

The liver parenchyma is organized as thousands of small (~0.7 × 2 mm) hepatic lobules in which hepatocytes form hundreds of irregular plates arranged radially around a small central vein (Figures 16–11 through 16–13). The hepatocyte

The liver, a large organ in the upper right quadrant of the abdomen, immediately below the diaphragm, is composed of thousands of polygonal structures called hepatic lobules, which are the basic functional units of the organ. (a) Diagram showing a small central vein in the center of a hepatic lobule and several sets of blood vessels at its periphery. The peripheral vessels are grouped in connective tissue of the portal tracts and include a branch of the portal vein, a branch of the hepatic artery, and a branch of the bile duct (the portal triad). (b) Both blood vessels in this triad branch as sinusoids, which run between plates of hepatocytes and drain into the central vein. (c) Micrograph of a lobule shows the central vein (C), plates of hepatocytes (H), and in an adjacent portal area a small lymphatic (L) and components of the portal triad: a portal venule (PV), hepatic arteriole (HA), and bile ductule (B). X220. H&E.
Liver

CHAPTER 16 Organs Associated with the Digestive Tract

■ Liver

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 lobules of some mammals, such as the pig, are delimited on all sides by connective tissue. (b) In humans these lobules have much less connective tissue and their boundaries are more difficult to distinguish. In both cases peripheral connective tissue of portal areas contains the portal triad: small bile ductules (D), venule (V) branches of the portal vein, and arteriole (A) branches of the hepatic artery. Both X150. H&E.

plates are supported by a delicate stroma of reticulin fibers (Figure 16–13b). Peripherally each lobule has three to six portal areas with more fibrous connective tissue, each of which contains three interlobular structures that comprise the portal triad (Figures 16–11 and 16–13d):

- A venule branch of the portal vein, with blood rich in nutrients but low in O2
- An arteriole branch of the hepatic artery that supplies O2
- One or two small bile ductules of cuboidal epithelium, branches of the bile conducting system.

Most of the peripheral portal areas also contain lymphatics and nerve fibers and in some species (eg, pigs) extend thin sheets of fibrous connective tissue completely around the lobules, making individual lobules easier to distinguish than in humans (Figure 16–12).

Between all of the anastomosing plates of hepatocytes of a hepatic lobule are important vascular sinusoids that emerge from the peripheral branches of the portal vein and hepatic artery and converge on the lobule’s central vein (Figures 16–11 through 16–13c). The venous and arterial blood mixes in these irregular hepatic sinusoids. The anastomosing sinusoids have thin, discontinuous linings of fenestrated endothelial cells surrounded by sparse basal lamina and reticular fibers. The discontinuities and fenestrations allow plasma to fill a narrow perisinusoidal space (or space of Disse) and directly bathe the many irregular microvilli projecting from the hepatocytes into this space (Figure 16–14). This direct contact between hepatocytes and plasma facilitates most key hepatocyte functions that involve uptake and release of nutrients, proteins, and potential toxins.

Two other functionally important cells are found with the sinusoids of hepatic lobules:

- Numerous specialized stellate macrophages, usually called Kupffer cells, are found within the sinusoid lining (Figure 16–15). These cells recognize and phagocytose aged erythrocytes, freeing heme and iron for reuse or storage in ferritin complexes. Kupffer cells are also antigen-presenting cells and remove any bacteria or debris present in the portal blood.

- In the perisinusoidal space are hepatic stellate cells (or Ito cells) with small lipid droplets that store vitamin A
Hepatocytes (H) are polygonal epithelial cells that form branching, irregular plates separated by venous sinusoids (S). H&E X400.

Reticulin (collagen type III) fibers (R) running along the plates of hepatocytes (H), supporting these and the intervening sinusoids. Most connective tissue in the liver is found in the septa and portal tracts. X400. Silver.

With plates of hepatocytes (H) appearing to radiate from it, the central vein (C) of the lobule has more collagen than the smaller sinusoids (S) that drain into it from all directions (arrows). X200. Mallory trichrome.

Peripheral portal areas contain more connective tissue and are the sites of the portal triad: a portal venule (PV), an arteriole branching off the hepatic artery (HA), and one or two bile ductules (BD). X200. H&E.

The endothelium of the central vein in the middle of each hepatic lobule is supported by a very thin layer of fibrous connective tissue (Figure 16–13c). Central venules from each lobule converge into larger veins, which eventually form two or more large hepatic veins that empty into the inferior vena cava.

and other fat-soluble vitamins (Figure 16–15b). These mesenchymal cells, which are difficult to see in routine preparations, also produce extracellular matrix (ECM) components (becoming myofibroblasts after liver injury) and cytokines that help regulate Kupffer cell activity.
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 those of the centrilobular 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 glyco-
gen metabolism.

While the sinusoidal (basolateral) domains of hepa-
tocytes process nutrients and other blood components and secrete the plasma proteins, the smaller apical surfaces of the hepatocytes form bile canaliculi and are involved in exo-
crine secretion bile (Figures 16–14 and 16–16). Within the hepatic plates hepatocytes adhere firmly with desmosomes and junctional complexes. The apical surfaces of two adherent hepatocytes are grooved and juxtaposed to form the canalicu-
lus, sealed by tight junctions, into which bile components are secreted (Figure 16–14). These canaliculi are elongated spaces (total length >1 km) with lumens only 0.5-1 μm in diameter with large surface areas due to the many short microvilli from the constituent hepatocytes (Figures 16–14 and 16–16).

The bile canaliculi form a complex anastomosing network of channels through the hepatocyte plates that end near the portal tracts (Figures 16–11b and 16–17). The bile flow therefore progresses in a direction opposite to that of the blood, that is, from the center of the lobule to its periphery. Bile canaliculi are the smallest branches of the biliary tree or bile conducting system. They empty into bile canals of Hering (Figure 16–17) composed of cuboidal epithelial cells called cholangiocytes.

In the endothelial lining of the hepatic sinusoids are numerous specialized stellate macrophages or Kupffer cells that detect and phagocytose effete erythrocytes. (a) Kupffer cells (K) are seen as black cells in a liver lobule from a rat injected with particulate India ink. X200. H&E.

(b) In a plastic section, Kupffer cells (K) are seen in the sinusoid (S) between two groups of hepatocytes (H). They are larger than the flattened endothelial cells (E). Between the en-
dothe
t
e
endothelial and the hepatocytes is a very thin space called the perisinusoidal space (PS) of Disse, in which are located small hepatic stellate cells (HS), or Ito cells, that maintain the very sparse ECM of this compartment and also store vitamin A in small lipid droplets. These cells are numerous but are difficult to demonstrate in routine histologic preparations. X750. PT.

The short bile canals quickly merge in the portal areas with the bile ductules lined by cuboidal or columnar cholangiocytes and with a distinct connective tissue sheath. Bile ductules gradually merge, enlarge, and form right and left hepatic ducts leaving the liver.

Into the canaliculi hepatocytes continuously secrete bile, a mixture of bile acids (organic acids such as cholic acid), bile salts (the deprotonated forms of bile acids), electrolytes, fatty acids, phospholipids, cholesterol, and bilirubin. Some bile components are synthesized in hepatocyte SER, but most are taken up from the perisinusoidal space; all are quickly secreted into the bile canaliculi (Figure 16–16). Bile acids/salts have an important function in emulsifying the lipids in the duodenum, promoting their digestion and absorption.

Bilirubin is a pigmented breakdown product of heme that is released from splenic macrophages primarily, but also from Kupffer cells, and carried to hepatocytes bound to albumen. Released into the duodenum with bile, bilirubin is converted by intestinal bacteria into other pigmented products, some of which are absorbed in the intestinal mucosa to be processed and excreted again in the liver or excreted into urine by the kidneys. These bilirubin-related compounds give feces and urine their characteristic colors.
Figure 16–16  Hepatocyte ultrastructure and major functions.

A diagram of hepatocyte cytoplasmic organization, with major functions localized. (1) RER is primarily engaged in synthesis of plasma proteins for release into the perisinusoidal space. (2) Potentially toxic compounds, bilirubin (bound to albumin) and bile acids are taken up from the perisinusoidal space, processed by enzymes in the tubulovesicular system of the SER, and secreted into the bile canaliculi. (3) Glucose is taken up from the perisinusoidal space and stored in glycogen granules, with the process reversed when glucose is needed.

Figure 16–17  Bile ductules.

Near the periphery of each hepatic lobule, many bile canaliculi join with the much larger bile canals of Hering, which are lined by cuboidal epithelial cells called cholangiocytes. These canals soon join the bile ductules in the portal areas and drain into the biliary tree.

Structure & Function in the Liver

As mentioned previously, hepatocytes are highly versatile cells with diverse functions that are reflected in their structure (Figure 16–16). Abundant rough ER is focused on synthesis of plasma proteins and causes cytoplasmic basophilia, which is often more pronounced in hepatocytes near the portal areas (Figure 16–12). Abundant smooth ER, distributed more evenly throughout the cytoplasm, contains the enzyme systems for the biotransformation or detoxification of substances in blood, which are then usually excreted with bile. These include enzymes responsible for oxidation, methylation, and conjugation of steroids, barbiturates, antihistamines, anticonvulsants, and other drugs. Under some conditions prolonged presence of drugs can lead to increased amounts of SER in hepatocytes, thus improving the liver's detoxification capacity. Other SER enzymes (glucuronosyl transferases) conjugate...
bile pigments, rendering it more soluble and facilitating its excretion in bile. Glycogen granules and small lipid droplets in hepatocytes, and very small electron-dense ferritin complexes (hemosiderin) primarily in the Kupffer cells, respectively, mediate temporary storage of glucose, triglycerides, and iron. Hepatocyte peroxisomes are also abundant and important for oxidation of excess fatty acids, catalase-mediated breakdown of the hydrogen peroxide generated by fatty acid oxidation (by means of catalase activity), and conversion of excess purines to uric acid. Many Golgi complexes are also present, involved in synthesis of both plasma proteins and bile components. The numerous mitochondria provide energy for all these activities (Figure 16–16).

**MEDICAL APPLICATION**

Fatty liver disease is a reversible condition in which large lipid droplets containing triglycerides accumulate abnormally in hepatocytes via the process called steatosis. This disorder has multiple causes, but it occurs most commonly in individuals with alcoholism or obesity. Accumulation of fat in hepatocytes may produce a progressive inflammation of the liver, or hepatitis, in this case called steatohepatitis.

The different categories of hepatocyte functions—including secretion of proteins into blood, the exocrine secretion of bile, and the removal of diverse small compounds from blood—have led to three ways of considering liver lobe structure, which are summarized in Figure 16–18.

- The classic hepatic lobule (Figure 16–18a), with blood flowing past hepatocytes from the portal areas to a central venule, emphasizes the endocrine function of the structure for uptake by plasma.
- The concept of portal lobules of hepatocytes is more useful when considering the exocrine function of these cells, that is, bile secretion. The portal area has the bile ductule at the center, and bile, moving in the opposite direction as the blood, flows toward it from all the surrounding hepatocytes. The tissue draining bile into each portal area duct is roughly triangular in shape, with the central veins of three classic lobules at its angles (Figure 16–18b).
- The hepatic acinus, a third way of viewing liver cells, emphasizes the nature of the blood supply to the hepatocytes and the oxygen gradient from the hepatic artery branch to the central vein. In a liver acinus hepatocytes make up an irregular oval or diamond-shaped area extending from two portal triads to the two closest central veins (Figure 16–18c). Periportal hepatocytes nearest the hepatic arteriole, comprising zone I in the acinus, get the most oxygen and nutrients and can most readily carry out functions requiring oxidative metabolism such as protein synthesis. Hepatocytes in zone III, near the central vein, get the least oxygen and nutrients. They are the preferential sites of glycolysis, lipid formation, and drug biotransformations and are the first hepatocytes to undergo fatty accumulation and ischemic necrosis. In the intervening zone II, hepatocytes have an intermediate range of metabolic functions between those in zones I and III. The major activities in any given hepatocyte result from the cell adapting to the microenvironment produced by the contents of the blood to which it is exposed.

**MEDICAL APPLICATION**

An important function of hepatocyte SER is the conjugation of hydrophobic (water-insoluble), yellow bilirubin by glucuronosyl transferases to form water-soluble, nontoxic bilirubin glucuronide, which is excreted into the bile canaliculi. When bilirubin glucuronide is not formed or excreted properly, various diseases characterized by jaundice can result.

A frequent cause of jaundice in newborns is an underdeveloped state of the hepatocyte SER (neonatal hyperbilirubinemia). A treatment in these cases is exposure to blue light from ordinary fluorescent tubes, which transforms unconjugated bilirubin into a water-soluble photosomer that can be excreted by the kidneys.

Unlike the salivary glands and pancreas, the liver has a strong capacity for regeneration despite its normal slow rate of cell renewal. Hepatocyte loss from the action of toxic substances triggers mitosis in the remaining healthy hepatocytes in a process of compensatory hyperplasia that maintains the original tissue mass. Surgical removal of a liver portion produces a similar response in the hepatocytes of the remaining lobe(s). The regenerated liver tissue is usually well organized, with the typical lobular arrangement, and replaces the functions of the destroyed tissue. This regenerative capacity is important clinically because one major liver lobe can sometimes be donated by a living relative for surgical transplant and full liver function restored in both donor and recipient.

Besides proliferation of existing hepatocytes, a role for liver stem cells in regeneration has been shown in some experimental models. Such cells, often called oval cells, are present among cholangiocytes of the bile canals near portal areas and produce progenitor cells for both hepatocytes and cholangiocytes.

**MEDICAL APPLICATION**

Most malignant tumors of the liver derive from hepatocytes or cholangiocytes of the hepatic ducts. Theogenesis of liver carcinoma is associated with a variety of acquired disorders, such as chronic viral hepatitis (B or C) and cirrhosis.
Studies of liver microanatomy, physiology, and pathology have given rise to three related ways to view the liver's organization, which emphasize different aspects of hepatocyte activity.

(a) The **classic lobule** concept offers a basic understanding of the structure-function relationship in liver organization and emphasizes the endocrine function of hepatocytes as blood flows past them toward the central vein.

(b) The **portal lobule** emphasizes the hepatocytes' exocrine function and the flow of bile from regions of three classic lobules toward the bile duct in the portal triad at the center here. The area drained by each bile duct is roughly triangular.

(c) The **hepatic acinus** concept emphasizes the different oxygen and nutrient contents of blood at different distances along the sinusoids, with blood from each portal area supplying cells in two or more classic lobules. Major activity of each hepatocyte is determined by its location along the oxygen/nutrient gradient: periportal cells of zone I get the most oxygen and nutrients and show metabolic activity generally different from the pericentral hepatocytes of zone III, exposed to the lowest oxygen and nutrient concentrations. Many pathologic changes in the liver are best understood from the point of view of liver acini.


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**BILIARY TRACT & GALLBLADDER**

The bile produced by the hepatocytes flows through the bile canaliculi, bile ductules, and bile ducts. These structures gradually merge, forming a converging network that ultimately forms the common hepatic duct, a common cystic duct from the gallbladder. All continue to the duodenum as the common bile duct (Figure 16–19).

The hepatic, cystic, and common bile ducts are lined with a mucous membrane having a simple columnar epithelium of cholangiocytes. The lamina propria and submucosa are relatively thin, with mucous glands in some areas of the cystic duct, and surrounded by a thin muscularis. This muscle layer becomes thicker near the duodenum and finally, in the duodenal papilla, forms a sphincter that regulates bile flow into the small bowel.

The gallbladder is a hollow, pear-shaped organ (Figure 16–19) attached to the lower surface of the liver, capable of storing 30-50 mL of bile that is concentrated during storage. The wall of the gallbladder consists of a mucosa composed of simple columnar epithelium and lamina propria, a thin muscularis with bundles of muscle fibers oriented in several directions, and an external adventitia or serosa (Figure 16–20a). The mucosa has numerous folds that are particularly evident when the gallbladder is empty.

The lining epithelial cells of the gallbladder have prominent mitochondria, microvilli, and large intercellular spaces, all indicative of cells actively transporting water, in this case for concentrating bile (Figure 16–20b). The mechanism for this includes activity of Na⁺ pumps in the basolateral membranes, followed by passive movement of water from the bile. To move stored bile into the duodenum, contraction of the gallbladder...