8.4 Pancreatic and Biliary Secretion

Learning Objectives

- List the endocrine secretions of the pancreas
- List the four major classes of exocrine secretions of the pancreas
- Identify in a drawing: the acinar cells, intralobular duct, interlobular duct, and main pancreatic duct
- List the proteolytic secretions of the pancreas
- Explain why the pancreas does not digest itself with its proteolytic secretions
- List the amylolytic secretions of the pancreas
- List the lipolytic secretions of the pancreas
- Describe the composition of the watery secretion of the pancreas, especially noting its pH
- Define what is meant by CFTR; note its subcellular location and function
- List three phases of regulation of pancreatic secretion
- Describe CCK: include its chemical nature, site of secretion, secretagogues, and actions
- Describe secretin: include its chemical nature, site of secretion, secretagogues, and actions
- Identify in a drawing: hepatic bile duct, cystic duct, gallbladder, common bile duct, and sphincter of Oddi
- List the major components of bile
- Name the primary and secondary bile acids and identify their source for synthesis
- Describe the enterohepatic circulation of bile acids
- Describe the function of the gallbladder

THE EXOCRINE PANCREAS SECRETES DIGESTIVE ENZYMES AND HCO_3^-

The pancreas has both **exocrine** and **endocrine** functions. Exocrine glands are glands with ducts that secrete materials onto some surface—generally the skin, the gastrointestinal tract, or respiratory epithelium. Endocrine glands are ductless and secrete hormones into the blood. The pancreas is both of these. Clusters of cells called the **islets of Langerhans**, distributed throughout the pancreas, secrete the hormones **insulin, glucagon**, and **somatostatin**, which regulate metabolism and the fate of absorbed nutrients. These endocrine functions are discussed in Chapter 9.4. The exocrine pancreas consists of clusters of **acini**, hollow spheroids of some 20–50 pyramidal cells arranged around a central lumen. The acini form lobules that are separated by loose connective tissue. Each acinus is drained by an intralobular duct which joins other ducts to form interlobular ducts and then progressively larger ducts until they reach the main pancreatic duct. The **acinar cells secrete protein enzymes that digest food**. The **ductal cells secrete a watery, alkaline solution** that neutralizes stomach acid and carries the enzymes forward (see Figure 8.4.1).

THE PANCREAS SECRETES FOUR CLASSES OF ENZYMES

The protein content of human pancreatic juice varies between 0.7% and 10% because of varying rates of secretion of protein and the watery solution that carries the proteins into the intestine. Digestive enzymes make up the major part of the protein secretion. Trypsin inhibitor, plasma proteins, and mucin make up the remainder. The pancreas secretes four classes of enzymes: **proteolytic enzymes**, **amylolytic enzymes**, **lipolytic enzymes**, and **nucleolytic enzymes**.

THE PANCREAS SECRETES INACTIVE FORMS OF THE PROTEOLYTIC ENZYMES

The pancreas secretes a set of proteolytic enzymes in an inactive form. These inactive forms include the following:

- Trypsinogen
- Chymotrypsinogen
- Proelastase
- Procarboxypeptidase A
- Procarboxypeptidase B.

Enterokinase, an enzyme secreted by the duodenal mucosa, converts trypsinogen to **trypsin**, which then autocatalytically converts more trypsinogen to trypsin. Trypsin then converts chymotrypsinogen to **chymotrypsin**, proelastase to **elastase**, and procarboxypeptidase A and B to **carboxypeptidase A and B**. Trypsin, chymotrypsin, and elastase are all endopeptidases: they hydrolyze peptide bonds on the interior of a protein. Carboxypeptidases A and B are exopeptidases: they cleave amino acids off the end of proteins. Carboxypeptidases split one amino acid at a time off the carboxyl end of a polypeptide chain. Carboxypeptidase A releases neutral amino acids and carboxypeptidase B releases cationic amino acids.

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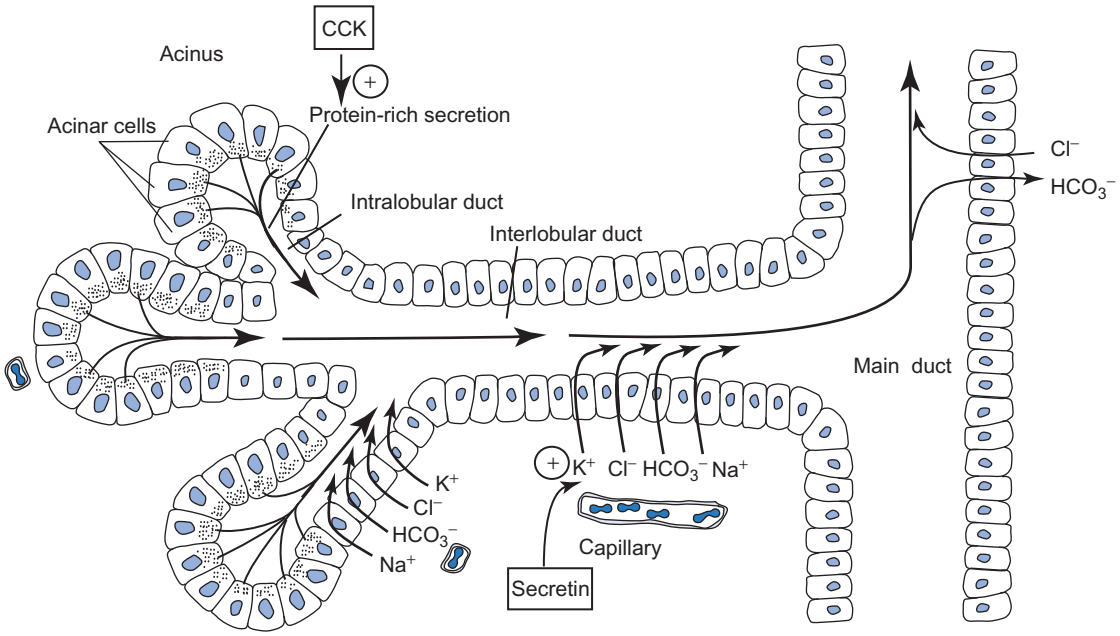

FIGURE 8.4.1 Schematic cartoon of the exocrine pancreas. The acinar cells store protein secretions in **zymogen granules**. Fusion of the granules with the apical membrane releases the enclosed proteins into the lumen of the acinus. **CCK** stimulates enzyme secretion. The interlobular duct cells' secretion is isoosmotic with plasma. **Secretin** stimulates secretion by the duct cells. As the fluid flows down the main pancreatic ducts, HCO_3^- exchanges for Cl^-.

The pancreas secretes small amounts of **trypsin inhibitor**. Between pH 3 and 7, this material forms a 1:1 complex with trypsin that inactivates its proteolytic activity. This protects the pancreas from being digested by small amounts of active trypsin, and it also prevents the premature activation of all of the other proteolytic enzymes. This inhibitor does not prevent activity of trypsin in the intestinal lumen because it is secreted in small amounts that are overwhelmed when trypsin becomes fully activated.

PANCREATIC AMYLASE BREAKS DOWN STARCHES

Most of the digestion of carbohydrates occurs on the brush border membrane of the **enterocytes**, the absorptive cells that line the villi. However, the salivary glands and the pancreas secrete distinct forms of **amylase**. This enzyme hydrolyzes the α-1,4-glycosidic bond in starch, but cannot hydrolyze the α-1,6-glycosidic bonds at which the starch chain branches, nor can it hydrolyze the β-1,4 linkages present in cellulose. See Chapter 8.5 for details about carbohydrate digestion and absorption. Amylase is secreted in its active form.

THE PANCREAS SECRETES A SET OF LIPOLYTIC ENZYMES

The pancreas secretes a variety of lipolytic enzymes, including:

- Pancreatic lipase
- Pancreatic colipase
- Phospholipase A_2
- Cholesterol esterase.

The role of these enzymes in lipid digestion and absorption is discussed in Chapter 8.5. The optimal activity of these enzymes depends upon the bile acids delivered to the intestine through the bile.

THE PANCREAS SECRETES NUCLEOLYTIC ENZYMES

The pancreas also secretes pancreatic **ribonuclease (RNAase)** and pancreatic **deoxyribonuclease (DNAase)**. These degrade nucleic acids in the ingested food.

PANCREATIC DUCT CELLS SECRETE AN ALKALINE SOLUTION IN TWO STAGES

The pancreas daily secretes 1−2 L of pancreatic juice that consists mainly of water, electrolytes, and pancreatic enzymes. The secretion occurs in two stages. The first phase consists of acinar secretion that makes up little volume but contains most of the pancreatic enzymes. Most of the fluid in the final pancreatic juice consists of ductal secretion that itself is different from secretion of the small and main pancreatic ducts. The acinar secretion is isoosmotic with plasma, and the major cations, Na^+ and K^+, are present in concentrations close to those in plasma, independent of the rate of pancreatic secretion. The major anions are Cl^- and HCO_3^-. In the main pancreatic duct, HCO_3^- is reabsorbed in exchange for Cl^-. Thus at high flow rates the $[HCO_3^-]$ is high because there is not enough time to exchange much HCO_3^- for Cl^-. At low flow rates, the $[HCO_3^-]$ and $[Cl^-]$ vary reciprocally (see Figure 8.4.2).

Figure 8.4.3 shows the main ion transport mechanisms involved with acinar secretion. The mechanisms of

secretion here are far less investigated that those in salivary glands, but, to the extent that they are known, the pancreatic acinar seem to use the same mechanisms as the salivary acini, with the noted absence of AQP5 from the apical membrane of pancreatic acini.

Pancreatic duct secretion differs from the acinar secretion in that the primary secretion is HCO_3^-. The secreted HCO_3^- derives from CO_2 in the circulation or from pancreatic cell metabolism, which is converted to HCO_3^- within the cells by the enzyme **carbonic anhydrase**. In the intralobular and small interlobular ducts, cells have a cAMP-regulated chloride channel in the apical membranes (those facing the lumen of the duct). This is the site of the defect in persons afflicted with **cystic fibrosis** and is called the **CFTR** for **cystic fibrosis transmembrane conductance regulator**. HCO_3^- secretion across the apical membrane depends on the Cl^- concentration in the lumen, which in turn depends on the activity of CFTR. The activity of CFTR is increased by cAMP, which is increased upon stimulation of the duct cells with **secretin**. Na^+ and K^+ in the ductal fluid arrive through **paracellular** pathways—between the cells and through the junctions at their apical ends rather than through the cells themselves. The pathway through the cells is called the **transcellular** pathway. The main idea here is that the pancreatic ducts secrete a highly alkaline fluid, and they accomplish this by secreting HCO_3^- and acidifying the blood. Figure 8.4.4 illustrates pancreatic duct secretion.

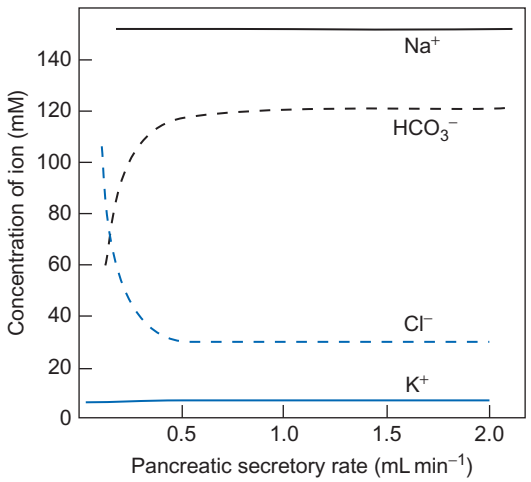

FIGURE 8.4.2 Concentration of pancreatic juice electrolytes as a function of secretory rate. The composition of the initial secretion in the acini is similar to plasma with high $[Na^+]$ and low $[K^+]$, but instead of high $[Cl^-]$ there is a high $[HCO_3^-]$. At high flow rates, the final pancreatic secretion retains these characteristics. At low flow rates, the HCO_3^- exchanges with Cl^- in the larger pancreatic ducts, and so the $[HCO_3^-]$ falls and $[Cl^-]$ rises.

POSTPRANDIAL PANCREATIC ENZYME SECRETION IS REGULATED IN *CEPHALIC, GASTRIC,* AND *INTESTINAL* PHASES

CEPHALIC INPUTS ACCOUNT FOR UP TO 50% OF MAXIMAL PANCREATIC ENZYME SECRETION

The sight, smell, and taste of food stimulate pancreatic secretion rich in enzymes. In humans, this effect can produce rates of secretion up to 50% of the maximal rates produced by infusion of secretin and

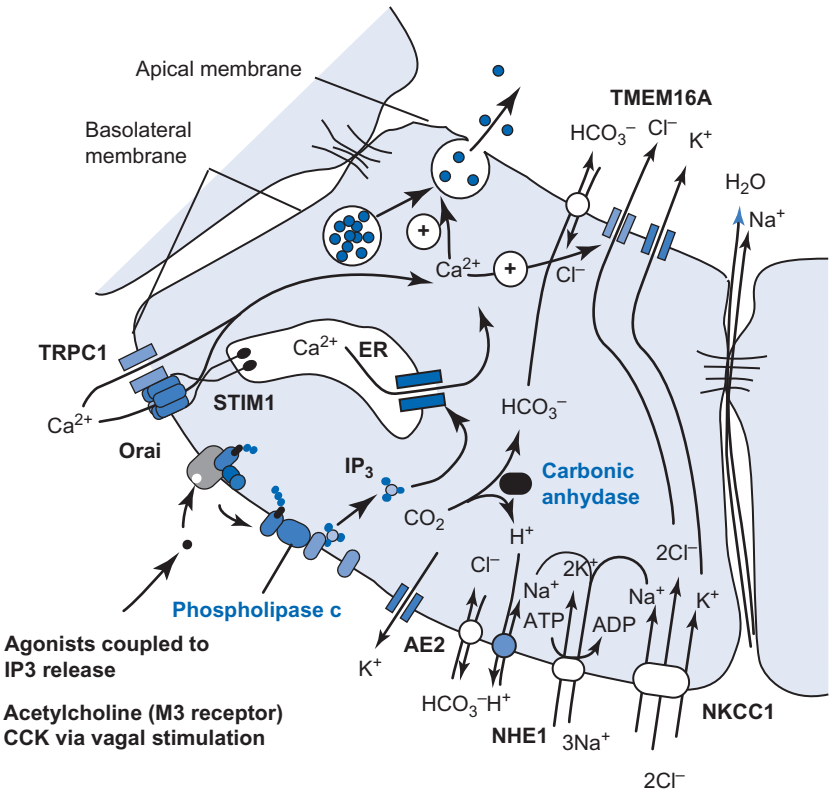

FIGURE 8.4.3 Mechanism of pancreatic acinar secretion. Secretion is stimulated mainly by parasympathetic stimulation mediated by cholinergic M3 receptors that operate via a G_q mechanism. CCK stimulates zymogen secretion mainly by activating vagal afferents that eventually release acetylcholine onto the acinar cells. Release of Ca^{2+} from the ER stimulates further influx of Ca^{2+} from the extracellular fluid through store-operated calcium entry (SOCE) involving STIM1 as a sensor of ER Ca^{2+} depletion and Orai and TRPC1 as routes of Ca^{2+} entry. Increased Ca^{2+} stimulates zymogen secretion and also activates an apical Cl^- channel and basolateral K^+ channels. Cl^- for secretion is provided by the Na–K–2Cl transporter (NKCC1) on the basolateral membrane, whose influx is made possible by the Na^+ gradient established by the Na,K-ATPase pump, also located on the basolateral membrane. The enzyme carbonic anhydrase provides HCO_3^- that is secreted in exchange for Cl^- at the apical membrane. The H^+ produced by the carbonic anhydrase is removed from the cell in exchange for Na^+ over the Na–H exchanger (NHE1) on the basolateral membrane. Water and Na^+ follow the transepithelial electrical potential and osmotic pressure of secreted solutes. The anion exchanger AE2 is present on the basolateral membrane and may either provide Cl^- or HCO_3^- for secretion into the lumen.

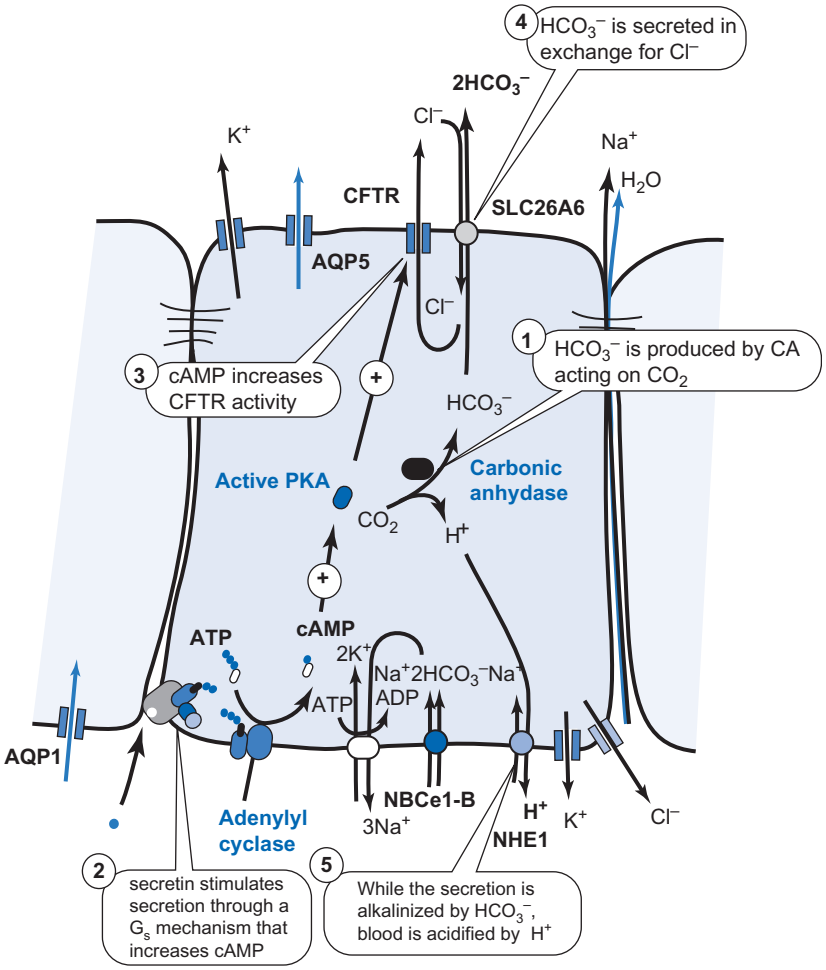

FIGURE 8.4.4 Mechanism of pancreatic duct cell secretion of electrolytes and water. CO_2 in the blood diffuses into the cell where it is hydrated by carbonic anhydrase (CA) to form H^+ and HCO_3^-. The HCO_3^- formed feeds into a HCO_3^-–Cl^- exchanger located in the apical cell membrane. This HCO_3^-–Cl^- exchanger is coupled to an apical membrane Cl^- channel that recirculates the Cl^-. This apical Cl^- channel is the cystic fibrosis transmembrane conductance regulator or CFTR. In its absence, the duct cells produce limited quantities of secretory fluid in a variety of epithelia including the pancreas and the respiratory epithelium, and the result is a thick, viscous, and sticky secretion. Na^+ and K^+ reach the lumen through paracellular pathways. The H^+ produced from the carbonic anhydrase acting on CO_2 exits the cell by exchange with Na^+, which in turn is pumped out of the cell by the Na^+, K^+-ATPase. The K^+ entering the cell by the Na^+, K^+-ATPase exits the cell through K^+ channels on the basolateral membrane Secretory HCO_3^- is also provided by a basolateral Na^+-HCO_3^- cotransporter, NBCe1-B. The co-transported Na^+ is removed by the basolateral Na^+-K^+-ATPase. Secretin stimulates ductal cell secretion by increasing the conductance of the apical CFTR. The mechanism involves stimulation of adenylyl cyclase through a G_s protein that increases cytoplasmic [cAMP].

cholecystokinin (CCK). The cephalic phase is mediated by vagus efferents to the pancreas. Acetylcholine stimulates pancreatic secretion through an M3 receptor, which activates a G_q protein that activates phospholipase C to release IP3 and DAG (diacylglycerol). The IP3 raises the cytosolic $[Ca^{2+}]$ by releasing Ca^{2+} from stores in the ER through the IP3 receptor (see Figure 8.4.3).

A VAGOVAGAL REFLEX MEDIATES THE GASTRIC PHASE OF PANCREATIC ENZYME SECRETION

Distension of the orad stomach, but not the antrum, stimulates pancreatic enzyme secretion. This effect is mediated by the vagus nerves and is abolished by vagotomy or atropine, an acetylcholine antagonist. This effect accounts for perhaps 5–10% of the postprandial pancreatic enzyme secretion in humans.

DELIVERY OF NUTRIENTS TO THE INTESTINE POWERFULLY STIMULATES PANCREATIC ENZYME SECRETION

Cholecystokinin or **CCK** is a peptide hormone secreted by endocrine I cells in the duodenal mucosa in response to amino acids and lipid digestion products in the duodenum. Recall from Chapter 8.2 that circulating CCK is a heterogeneous mixture of forms up to 83 amino acids in length. After a meal, fasting levels of CCK increase from 1 to 6–8 pM within 10–30 minutes. The CCK stimulates pancreatic zymogen secretion by activating vagal afferents in the duodenum. These afferents travel to the CNS and engage vagal efferents whose postganglionic fibers stimulate the acinar cells. Phenylalanine, valine, and methionine stimulate pancreatic enzyme secretion the most. Undigested fats do not release CCK, whereas fatty acids and monoglycerides effectively release CCK. In addition, sensory afferents detecting duodenal hyperosmolarity and stretch receptors initiate vagovagal reflexes that increase pancreatic enzyme secretion.

SECRETIN PRIMARILY REGULATES PANCREATIC DUCT SECRETION

Secretin is a linear polypeptide of 27 amino acids. S-cells located in the duodenum and proximal jejunum secrete secretin in response to increased $[H^+]$ in the lumen, mediated through the release of secretin releasing peptides from the duodenum. Secretin increases HCO_3^- secretion from the bile ducts and pancreatic ducts and from Brunner's glands in the intestine and delays gastric emptying and therefore the delivery of acid into the duodenum. This makes a neat feedback loop: the acid that stimulates secretin release is

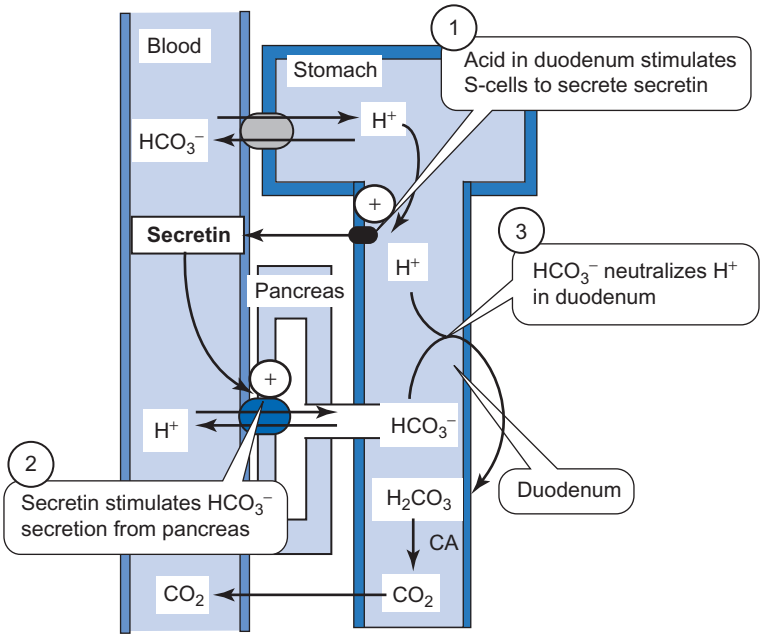

FIGURE 8.4.5 Negative feedback loop for H^+ in the duodenum. Parietal cells in the stomach secrete H^+ into the stomach while alkalinizing the blood with HCO_3^-. The acid in the stomach enters the duodenum where it stimulates S-cells to secrete secretin into the blood. Secretin stimulates pancreatic duct secretion of HCO_3^- by stimulating the CFTR through increasing cAMP. The secretion of HCO_3^- into the ducts is accompanied by acidification of the blood with H^+. The HCO_3^- secreted into the duodenum combines with, and neutralizes, the H^+ which entered from the stomach. In addition, the H^+ added to the blood by the pancreas is neutralized by the HCO_3^- added to the blood by the stomach.

neutralized by the HCO_3^- secreted in response to secretin. Secretin is linked to a G_s protein that increases cytosolic cAMP in its target cells by increasing the activity of adenylyl cyclase. The negative feedback of acid in the duodenum is shown in Figure 8.4.5.

THE LIVER PRODUCES BILE AND STORES IT IN THE GALLBLADDER IN THE INTERDIGESTIVE PERIOD

Bile is produced by the liver, which collects the bile first in **bile canaliculi** that drain just a few **hepatocytes**, or liver cells. These bile canaliculi drain into progressively larger bile ducts, eventually forming right and left hepatic bile ducts. These fuse into the **common hepatic duct**. The **cystic duct** comes off the common hepatic duct and leads to the **gallbladder**. The gallbladder is a small sac invested with smooth muscle that resides in a small indentation of the liver just above the duodenum. The continuation of the bile duct below the divergence of the cystic duct is called the **common bile duct**. It enters the duodenum alongside the pancreatic duct at the **ampulla of Vater**. The sphincter around the ampulla is the **sphincter of Oddi**. Figure 8.4.6 shows the anatomic arrangement of the **biliary tree**.

HEPATOCYTES ARE POLARIZED CELLS WITH SPECIAL ACCESS TO PLASMA

Hepatocytes are typically arranged in sheets of single cells that fan out from a **central vein** to form an **hepatic lobule**. The hepatocytes are polarized with a basolateral membrane facing the blood and an apical membrane facing the bile canaliculus. The canaliculus is defined by two adjoining cells, which are connected by junctional complexes. The liver is perfused with blood from the **hepatic portal vein**, which drains the intestines, and the **hepatic artery**. Venous blood drains into a central vein. In the liver, endothelial cells lack basement membranes, and this facilitates transfer of materials into the **space of Disse** between endothelial cells and hepatocytes and allows the hepatocytes to contribute to blood proteins and lipoproteins. Figure 8.4.7 illustrates the histological arrangement of the hepatocytes and the mechanism of bile formation. This figure illustrates how blood flow from the portal vein is countercurrent to the flow of bile. This arrangement is critical to the recirculation of bile acids during a meal.

BILE CONSISTS OF *BILE ACIDS, PHOSPHOLIPIDS, CHOLESTEROL, BILE PIGMENTS, MUCIN, XENOCHEMICALS,* AND *ELECTROLYTES*

The bile acids are actively secreted into the bile and function as emulsifying agents for the digestion of fats in the intestine (see Chapter 8.5). Bile also contains phospholipids and cholesterol that bind the bile acids and protect the cell from the cytotoxic detergent effects of bile acids. Mucin in the bile helps protect the epithelium lining the bile ducts from the damaging effects of the bile acids. The electrolytes in the bile exert an osmotic pressure that helps produce the flow of bile. The osmotic activity of the bile acids, phospholipids, and cholesterol is diminished because they aggregate to form large structures called **micelles**. The average composition of hepatic bile is described in Table 8.4.1.

THE LIVER MAKES AND RECYCLES BILE ACIDS AS AN INTEGRAL PART OF BILIARY SECRETION

Primary bile acids (**cholic acid** and **chenodeoxycholic acid**) are synthesized from cholesterol in hepatocytes.

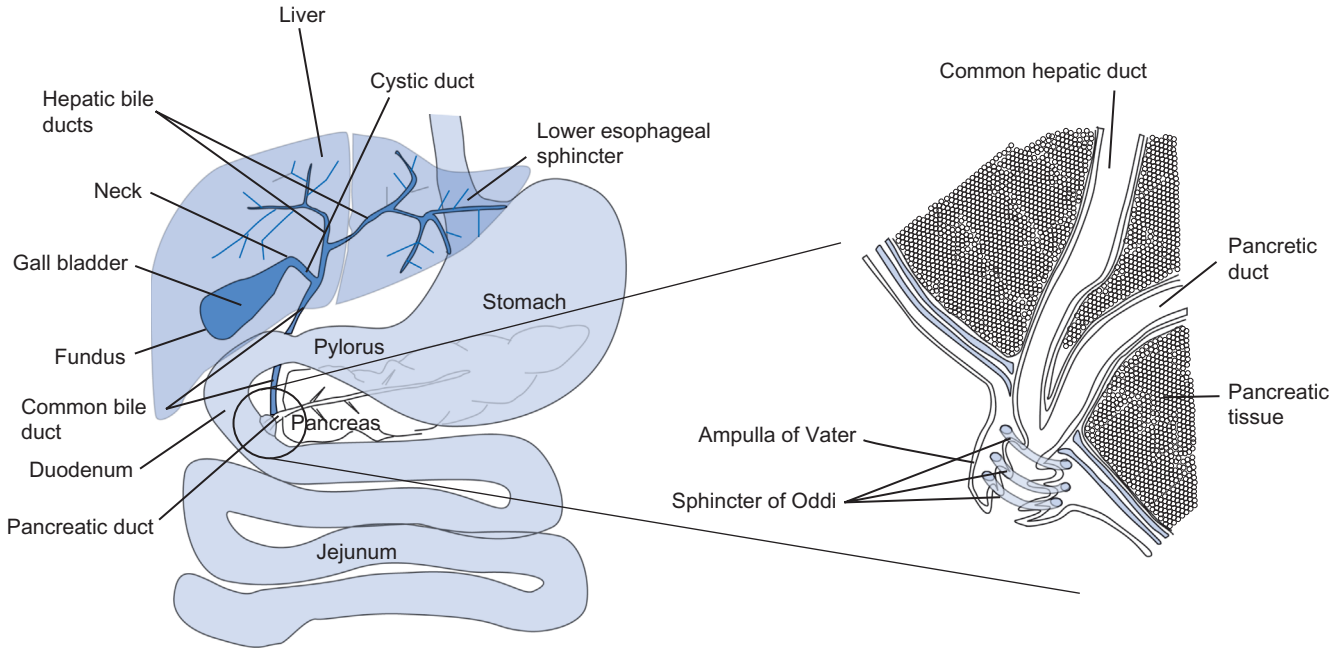

FIGURE 8.4.6 Anatomical structures of the biliary tree, with a close-up view of the hepatopancreatic junction with the duodenum.

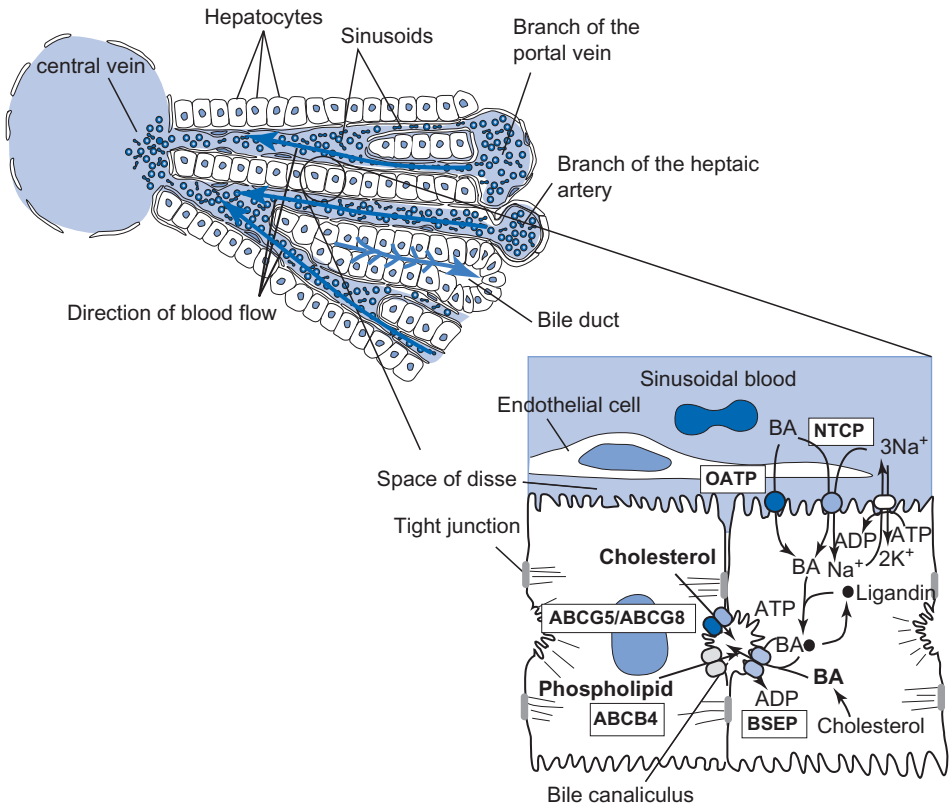

FIGURE 8.4.7 Hepatic lobule and close-up view of two hepatocytes. Bile is formed by the liver cell and placed into a bile canaliculus. These canaliculi aggregate to form progressively larger bile ductules, culminating in the right and left hepatic ducts. Bile acids (BA) are reclaimed from sinusoidal blood by a Na^+-dependent cotransporter (NTCP, Na^+-taurocholate cotransporting polypeptide, also known an SLC10A1) and Na^+-independent mechanisms (OATP, organic anion transporting protein = SCLO1B3). A family of cytosolic proteins called ligandins bind bile acids. The function of the ligandins in bile transport is unknown. They may protect the cell from the solubilizing effects of the bile acids or they may help in cytoplasmic transport of the bile acids. Bile acids derive mostly from uptake from the sinusoidal blood, but some is synthesized anew each day from cholesterol. The bile acids are actively secreted into the bile canaliculus via the bile salt export pump (BSEP) which is an ATP-binding casette transporter, known as ABCB11. Phospholipids are secreted by the multidrug resistant receptor 4 (MDR4), also known as ABCB4. Cholesterol is also secreted by an ATP-binding casette transporter. These ATP-binding casettes are all dimers that bind two ATP, one for each subunit, and hydrolyze them during the transport cycle. The BSEP and MDR4 are both homodimers; the cholesterol transporter is a heterodimer consisting of ABCG5 and ABCG8. The secreted phospholipids, cholesterol, and bile acids aggregate to form micelles within the bile.

The activity of a microsomal cholesterol 7 hydroxylase determines the rate of formation of the primary bile acids, and this enzyme is inhibited by bile acids. Thus the synthesis of the bile acids is under negative feedback control. This degradation of cholesterol is the largest metabolic sink for cholesterol in the body. The primary bile acids are secreted into the bile by a primary active transport mechanism, the bile salt export pump (BSEP = ABCB11) as described in Figure 8.4.7.

TABLE 8.4.1 Average Composition of Hepatic Bile

Components	Concentration (mM)
Na^+	140–165
K^+	3–7
Cl^-	77–117
HCO_3^-	12–55
Bile salts	3–45
Bilirubin	1–2
Phospholipids	140–810 mg%
Cholesterol	100–320 mg%

From R.H. Mosely, Bile Secretion, in T. Yamada, et al., eds., Textbook of Gastroenterology, *vol. I, Lippincott Williams and Wilkins, Philadelphia, PA, 1999.*

In the intestine, these primary bile acids are altered by intestinal bacteria to produce **secondary bile acids**: **lithocholic acid**, **deoxycholic acid**, and **ursodeoxycholic acid**. The bile acids are reabsorbed into the portal blood by the terminal ileum. This portal blood returns to the liver and the bile acids are taken up from the sinusoidal blood by a Na^+-dependent cotransporter that links bile acid uptake to Na^+ entry (NTCP = SLC10A1, see Figure 8.4.7) and by a second mechanism on the basolateral membrane that does not require Na^+ (OATP = SLCO1B3, see Figure 8.4.7). This recycling of bile acids from liver to intestine and back to liver is called the **enterohepatic circulation** (see Figure 8.4.8). The entire bile acid pool of the body may turn over three to five times during a single meal.

The liver conjugates the —COOH group of the bile acids by covalently linking it with glycine or taurine. This occurs after the synthesis of the primary bile acids and

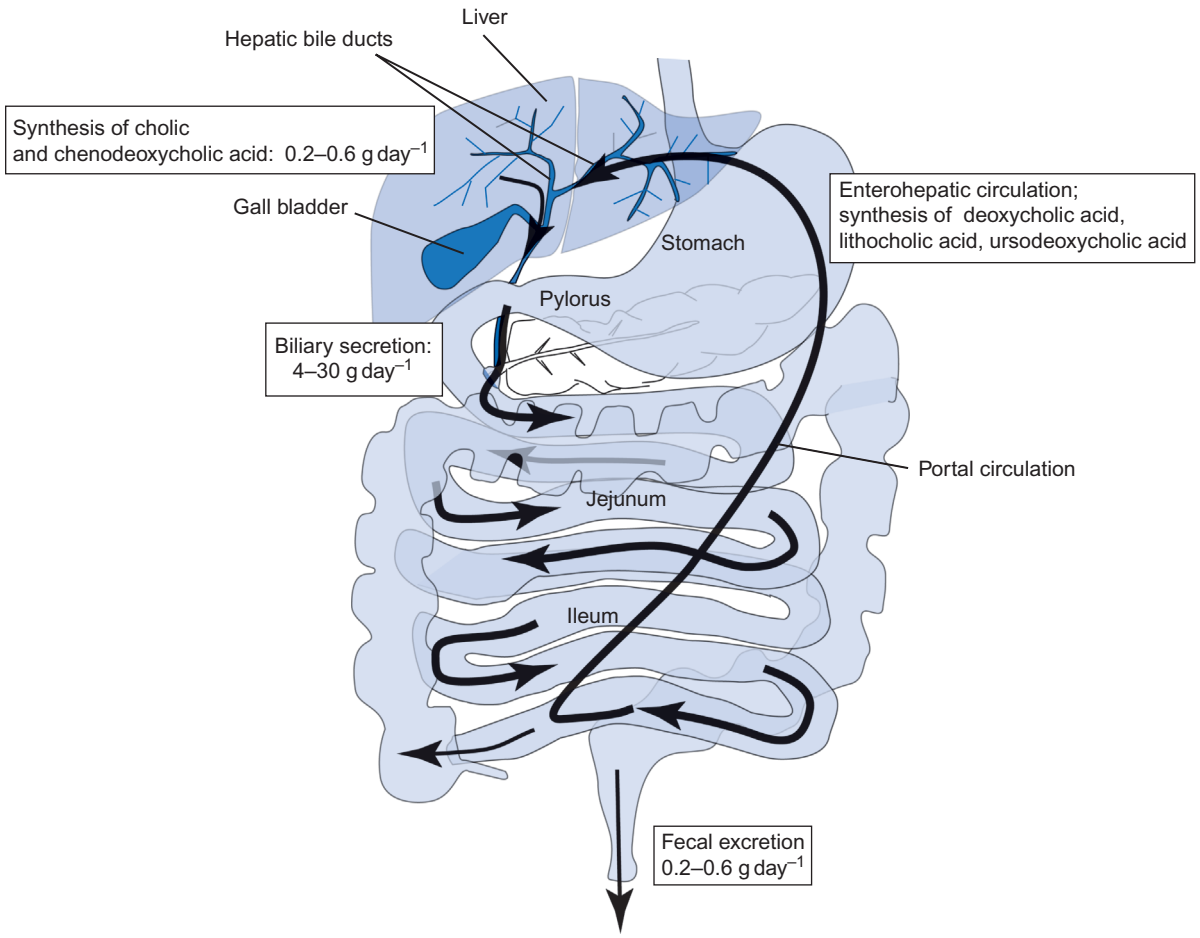

FIGURE 8.4.8 Enterohepatic circulation of the bile acids. Bile acids are synthesized in the liver, secreted into the bile, and stored temporarily in the gallbladder. After a meal, the gallbladder contracts and bile enters the duodenum at the sphincter of Oddi. Intestinal flora modifies the bile acids to form secondary bile acids. Both primary and secondary bile acids are absorbed into the portal blood at the terminal ileum. The liver takes up the bile acids from the portal blood and recycles them back into the bile. Numbers in boxes give the average bile acid amounts per day.

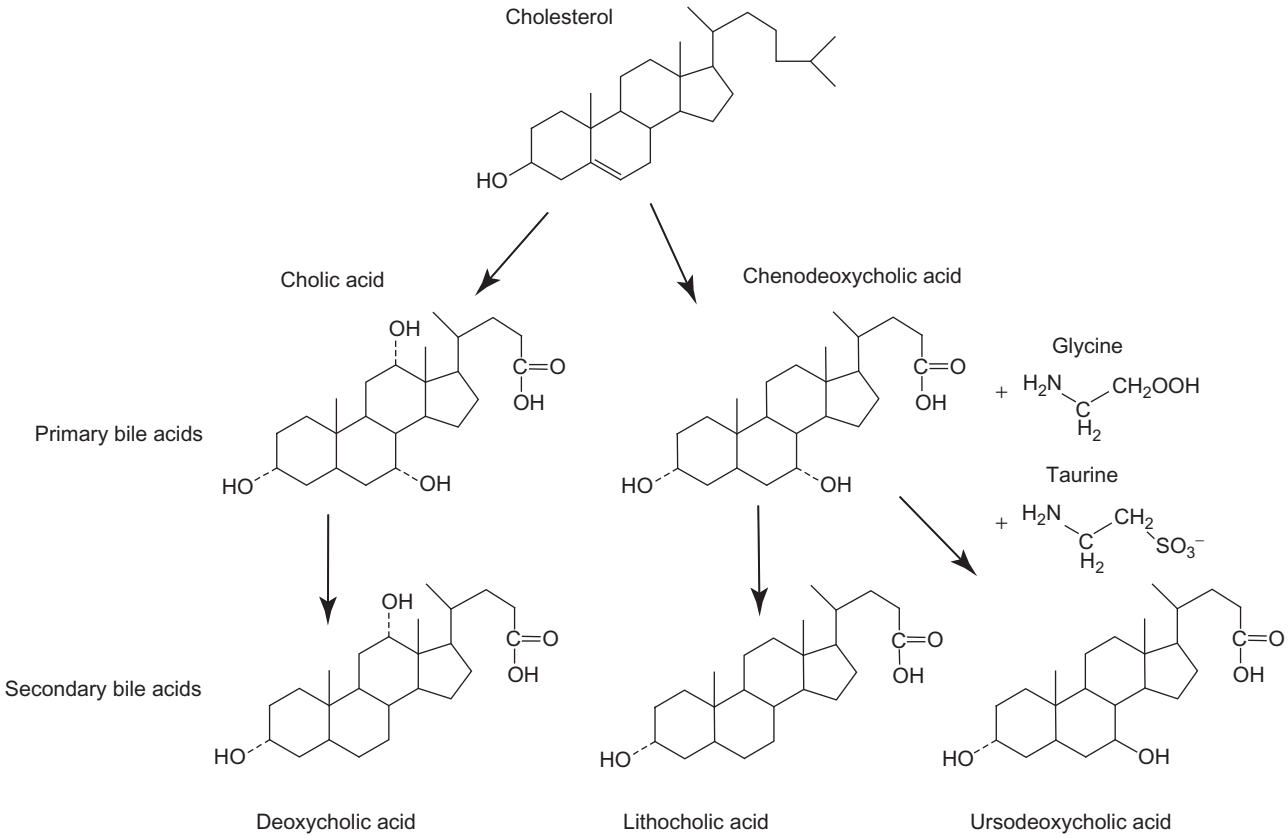

FIGURE 8.4.9 Structures of the primary and secondary bile acids. The primary bile acids are synthesized in the liver cells from cholesterol and are excreted into the bile as such. Intestinal bacteria convert the primary bile acids into secondary bile acids, which are reabsorbed along with unchanged primary bile acids in the terminal ileum.

during the hepatic phase of the enterohepatic circulation. Thus the bile contains cholic acid, glycocholic acid, taurocholic acid, and the corresponding free and conjugated forms of chenodeoxycholic acid, lithocholic acid, deoxycholic acid, and ursodeoxycholic acid. Figure 8.4.9 shows the chemical structures of the primary and secondary bile acids.

Bile acids have potent **surface activity** and can solubilize membrane proteins and lipids. They typically exhibit a **critical micellar concentration** or **CMC**. At low concentrations, below the CMC, the bile acids are monomers in solution. At higher concentrations, above the CMC, the bile acids aggregate to form micelles, small aggregates in which the hydrophilic hydroxyls of the bile acids face the water phase and the hydrophobic organic backbone of the steroid nucleus faces the interior of the micelle (see Chapter 8.5 for illustrations of these structures). In this form, the bile acids can absorb hydrophobic materials such as cholesterol and phospholipids to form **mixed micelles**. To prevent the bile acids from solubilizing the liver cells, the cytoplasmic bile acid concentration must be kept low. This is achieved by **ligandins**, a family of proteins that bind bile acids with high affinity. These ligandins have catalytic activity; they are glutathione S-transferases. But they also bind bile acids and bilirubin with high affinity. Their function in this regard is not established, but they probably protect the liver cell from the toxic effect of bile acids, while simultaneously carrying the bile acids to the bile canaliculus where the bile acids are excreted into the bile.

THE LIVER EXCRETES *XENOBIOTICS* (FOREIGN BIOLOGICALLY ACTIVE CHEMICALS)

The bile provides an excretory pathway for organic lipophilic xenobiotics such as drugs because these are not easily eliminated by the kidneys through the urine. Such compounds are poorly filtered by the glomerulus and are not readily secreted by the kidney tubules (see Chapter 7.2). The liver contains multispecific enzymes called **monooxygenases** of the **cytochrome P450** family. Their general reaction is to insert hydroxyl groups into foreign compounds as shown in Figure 8.4.10.

Drugs or other foreign compounds such as pesticides, plant alkaloids, and organic pollutants can be recognized by nonspecific transporters called **MDR**, for **m**ulti-**d**rug **r**esistance-associated protein. This protein is a member of a family of **ABC transporters**, so-named because each member of the family possesses an ATP-**b**inding **c**assette. These ABC transporters split ATP and transport a variety of materials across membranes. The MDR2 protein, also known as ABCB4, secretes phospholipids across the canalicular membrane.

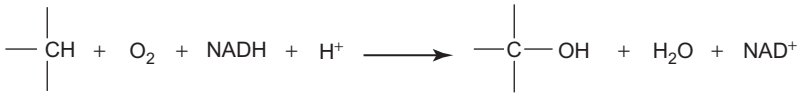

FIGURE 8.4.10 Generalized reaction of liver monooxygenases. These enzymes use NADH and molecular oxygen to hydroxylate a variety of lipophilic xenobiotics to make them more water soluble and more easily excreted either in the bile or in the urine.

ABCG5 AND ABCG8 SECRETE CHOLESTEROL INTO THE BILE

Cholesterol enters liver cell metabolism two ways: by synthesis from acetyl CoA or from import from blood-borne lipoproteins. Lipoproteins are complexes of lipid and proteins called apolipoproteins. Liver cells take up a variety of lipoproteins including chylomicron remnants, HDL (high-density lipoproteins), and LDL (low-density lipoproteins). Both newly synthesized and imported cholesterol can be exported from the cell into the bile across the bile canaliculus. Two ABC transporters, ABCG5 and ABCG8, form a heterodimer that transports cholesterol into the bile.

THE *GALLBLADDER* STORES AND CONCENTRATES BILE AND RELEASES IT DURING DIGESTION

The liver makes 0.5–1.0 L of bile per day. During the interdigestive periods, much of this is directed along the cystic duct to fill the gallbladder, which stores the bile and concentrates it. The gallbladder itself can hold only some 15–60 mL of fluid. The gallbladder absorbs water by actively pumping Na^+ out of the fluid. Cl^- and HCO_3^- are also absorbed, and water is drawn out of the bile by the osmotic pressure of the absorbed electrolytes. In this way, the gallbladder can concentrate the bile some 10-fold.

CCK is released from I cells in the mucosa of the duodenum in response to amino acids and fat digestion products. As described earlier, it increases the enzyme secretion of the pancreatic acinar cells. In addition, CCK stimulates contraction of the gallbladder and relaxation of the sphincter of Oddi. The effects of CCK on gallbladder contraction in the intact biliary tree are mediated by its stimulation of cholinergic nerves. Since CCK is released upon the entry of chyme into the duodenum, this action serves to deliver bile to the intestine when it is needed.

THE BILE DUCT CELLS SECRETE A HCO_3^--RICH SOLUTION MUCH LIKE PANCREATIC DUCT CELLS

The bile ducts secrete a watery fluid using the same mechanisms as the pancreatic ducts. As with the pancreatic ducts, secretin stimulates bile duct secretion through increasing cAMP in the ductal cells. Secretin is secreted from the duodenal mucosa S-cells primarily in response to duodenal acidification. The overall flow of bile consists of a **bile acid-dependent bile flow** and a second component that is independent of bile acid secretion and is attributed to the secretion of the electrolytes. This **bile acid-independent bile flow** is defined as the *Y*-intercept of the graph of bile flow against bile acid secretion, as shown in Figure 8.4.11.

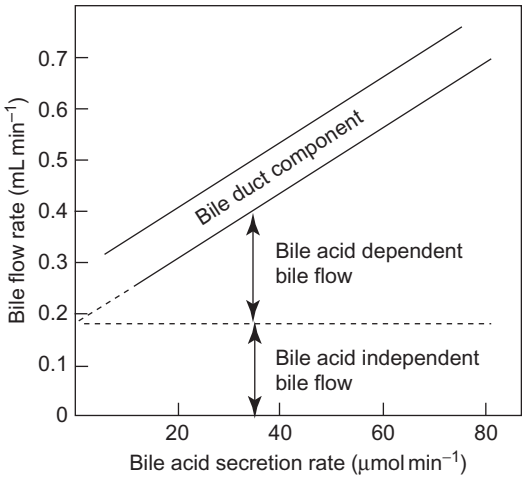

FIGURE 8.4.11 Components of bile flow. The actual relationship between biliary flow rate and bile acid secretion rate is probably curvilinear, but the diagram helps illustrate the division of bile flow into a bile acid-dependent flow and a bile acid-independent flow. On top of this flow, the bile ducts contribute fluid to augment the hepatic bile flow.

Clinical Applications: Gallstones

Gallstones come in several varieties, among which are cholesterol gallstones and pigment gallstones. Cholesterol gallstones contain 50–75% cholesterol and most contain a pigmented center that suggests that a pigment stone first formed and acted as a center for crystallization (or **nidus**) for cholesterol. Cholesterol by itself is nearly insoluble in water. It is transported in blood and in bile solely by its association with other materials that are soluble. Thus the solubility of cholesterol in bile depends entirely on the concentrations of bile acids and phospholipids that hold cholesterol in solution. The condition of having gallstones has the technical name **cholelithiasis**, which derives from the roots **chole** (bile) and **lith** (stone). Bile that is supersaturated with cholesterol is called **lithogenic** bile. In persons who form gallstones, the liver makes lithogenic bile, but how this unstable solution can be formed is not yet known. Persons susceptible to cholesterol gallstones generally (but not always!) fit a pattern of the four Fs: **f**at, **f**air, **f**orty, and **f**ertile.

Often cholesterol gallstones are asymptomatic and they are discovered accidentally during tests for other reasons. Asymptomatic or "silent stones" need no treatment. Gallstones may also provoke a gallbladder "attack" which may include

(*Continued*)

Clinical Applications: Gallstones (Continued)

steady pain in the upper abdomen, in the back between the shoulder blades, or under the right shoulder; nausea or vomiting; abdominal bloating; excessive belching; indigestion; and colic (cramping of gastrointestinal sections). Stones can sometimes lodge in the cystic duct, causing stagnant bile and **acute cholecystitis**. Blockade of the common bile duct by a stone can produce **cholangitis** and **jaundice.** Yellow pigments arise when blood is broken down, and normally the liver excretes these in the bile. If the bile cannot be excreted, or if the liver fails, these pigments accumulate and give a yellow cast to skin and eyes. This condition is called jaundice. In addition, stones blocking the lower end of the bile duct where it enters the intestine can obstruct pancreatic secretions leading to **acute pancreatitis**. Since bilirubin in the bile secretions produces the color of the stools, clay-colored stools indicate lack of biliary secretions into the gastrointestinal tract. Sweating, chills, or low-grade fever and jaundice in conjunction with the other symptoms require immediate medical attention.

Most symptomatic stones result in surgical removal of the gallbladder or **cholecystectomy**. This is one of the most common surgical procedures, with some 500,000 performed annually in the United States. Laparascopic cholecystectomy is most common and is used when there are no complications. This ordinarily does not seriously impair fat digestion because bile is still continuously produced by the liver. In some cases, the ability to digest dietary fat may be reduced. Other treatments include **oral dissolution therapy** in which cholesterol gallstones are dissolved by increasing the bile acid content of the bile by orally ingesting ursodeoxycholic acid (Actigall) or chenodeoxycholic acid (Chenix). Such therapy may take months or years to dissolve stones, and the stones will recur unless medication is continued for life. Small stones can be broken into tiny parts by **extracorporeal shockwave lithotripsy**, and the small stones can be passed into the gastrointestinal tract through the bile ducts. Shock waves are produced by an underwater high voltage discharge and the concentration of shock waves is achieved by reflection. Oral bile acid therapy prevents the recurrence of gallstones following lithotripsy. Extracorporeal shockwave lithotripsy is only sparingly used. Presently, the overwhelmingly favored treatment of symptomatic gallstones is cholecystectomy.

SUMMARY

The pancreas has both endocrine and exocrine functions. It produces the hormones insulin, glucagon, and somatostatin and also an exocrine secretion of a watery solution containing digestive enzymes. The exocrine acini produce and secrete proteolytic enzymes including trypsinogen, chymotrypsinogen, proelastase, and procarboxypeptidases A and B. These forms are all inactive and are activated in the intestine by a cascade begun by enterokinase that activates conversion of trypsinogen to trypsin. The pancreas also produces a trypsin inhibitor to prevent premature activation of trypsinogen within the pancreas. The pancreas also produces pancreatic amylase to digest starch, pancreatic lipase and co-lipase, phospholipase A_2, cholesterol esterase, RNAase, and DNAase.

The pancreas produces a watery solution that is rich in HCO_3^-. Secretin is released from the duodenum in response to acid, and secretin increases the activity of the CFTR (cystic fibrosis transmembrane conductance regulator) in the apical membranes of acinar cells. The CFTR secretes Cl^- which then drives HCO_3^- secretion through an exchange mechanism. Thus secretin increases the pancreatic secretion of a HCO_3^--rich solution. As the fluid flows down the pancreatic ducts, the HCO_3^- is exchanged for Cl^-, so that the composition of the pancreatic secretion depends on its flow rate: at high rates the HCO_3^- remains high because there is insufficient time for complete exchange for Cl^-.

Vagal efferents control pancreatic enzyme secretion that results from the sight, smell, and taste of food. CCK increases pancreatic secretion that results from food in the duodenum. Fat digestion products and amino acids potently stimulate CCK release from the duodenum, which excites vagal afferents to begin a vagovagal reflex to stimulate pancreatic enzyme secretion.

Bile consists of a HCO_3^--rich solution that contains bile pigments derived from blood breakdown products, mucin, bile acids, cholesterol, phospholipids, electrolytes, and detoxified xenochemicals. Bile is produced in the liver by the hepatocytes and collected first into tiny canaliculi, which progressively fuse to form the hepatic bile duct. The gallbladder stores and concentrates bile during interdigestive periods and releases it during meals. The cystic duct branches off the hepatic duct to fill the gallbladder. The common bile duct enters the duodenum at the ampulla of Vater. The sphincter of Oddi controls the opening of this duct. After a meal, the duodenum releases CCK that stimulates gallbladder contraction and relaxation of the sphincter of Oddi. The bile acids in the bile help digest and absorb fats.

The liver makes primary bile acids, cholic acid, and chenodeoxycholic acid, from cholesterol. In the intestine, bacteria convert these to secondary bile acids, lithocholic acid, deoxycholic acid, and ursodeoxycholic acid. These are absorbed into the blood at the terminal ileum and come back to the liver in the portal circulation. Thus the primary and secondary bile acids are recirculated. The recycling of the bile acids is called the enterohepatic circulation. The entire bile acid pool may turn over several times during a single meal.

REVIEW QUESTIONS

1. What exocrine secretions does the pancreas make? Where do these things go?
2. What are the three phases of pancreatic secretion? What mediates them? What are the initial sensory stimuli in each case?
3. Where is bile formed? Trace its flow from liver to duodenum.
4. What is meant by "primary" bile acids and "secondary" bile acids? Which bile acids are primary

and which are secondary? How do the secondary bile acids get into the bile?

5. What is the "enterohepatic circulation"? Where are bile acids absorbed in the gastrointestinal tract?
6. What else is in bile besides the bile acids?
7. Some amount of circulating cholesterol is absorbed from dietary sources. This absorption requires the bile acids to solubilize the cholesterol in the gut so it can be absorbed. Cholestyramine is an ion-exchange resin that binds bile acids and therefore interferes with the enterohepatic circulation. Since bile acids are necessary for dietary cholesterol absorption and also are the main sink for cholesterol in the body, ingesting cholestyramine should lower blood cholesterol. Do you anticipate any negative side effects of cholestyramine ingestion?
8. What does the gallbladder do? What happens if you remove it (cholecystectomy) due to gallstones?
9. What is the main stimulus for gallbladder contraction?