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The Biliary System

Second Edition

David Q.-H. Wang
Brent A. Neuschwander-Tetri
Piero Portincasa

Colloquium Lectures on
Integrated Systems Physiology
From Molecule to Function to Disease

Series Editors: *D. Neil Granger & Joey Granger*

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COLLOQUIUM SERIES ON INTEGRATED SYSTEMS PHYSIOLOGY: FROM MOLECULE TO FUNCTION TO DISEASE #71

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ABSTRACT

The liver is a vital organ involved in numerous metabolic processes such as cholesterol and bile acid metabolism, biliary lipid secretion, and bile formation. Cholesterol balance across the liver has a crucial effect on influencing plasma total and LDL cholesterol levels and biliary cholesterol concentrations. Cholesterol and bile acid biosyntheses are primarily modulated by negative feedback regulatory mechanisms through the sterol regulatory element-binding protein isoform 2 (SREBP-2) and the farnesoid X receptor (FXR) pathways, respectively. The conversion of cholesterol to bile acids in the liver can balance the fecal excretion of bile acids, which is an important route for the removal of cholesterol from the body. Bile formation begins in the bile canaliculi, and maintenance of the enterohepatic circulation of bile acids results in a continuous secretion of bile. Hepatic secretion of biliary lipids is determined mainly by a group of ATP-binding cassette (ABC) transporters that are located on the canalicular membrane of hepatocytes, which are regulated by various nuclear receptors. Bile acids promote bile flow by their osmotic effects. Also, they are essential for the intestinal absorption of cholesterol, fatty acids, and fat-soluble vitamins and play an important role in aiding the digestion of dietary fat. Bile acids function as signaling molecules and anti-inflammatory agents to regulate lipid, glucose, and energy metabolism by rapidly activating nuclear receptors and cell signaling pathways. This eBook summarizes the progress in the molecular and cellular mechanisms of cholesterol and bile acid metabolism and the physical-chemistry of biliary lipids, with emphasis on biliary lipid metabolism that is regulated by nuclear receptors in the hepatobiliary system.

KEY WORDS

bile, cholesterol synthesis, bile acid metabolism, biliary secretion, enterohepatic circulation, hepatic lipid transporter

Contents

Preface

Research on the hepatobiliary system in health and disease is rapidly growing. The exponential expansion of this body of knowledge reveals the complex molecular and cellular mechanisms determining lipid trafficking as an essential part of the overall body metabolism. The liver plays a critical role in the synthesis of cholesterol and its conversion to bile acids, as well as in biliary secretion of these lipids. The liver is also at the crossroads of complex metabolic processes, which include uptake of chylomicrons of intestinal origin by the hepatocytes, as well as uptake, synthesis, and secretion of plasma apolipoproteins and lipoproteins that shuttle cholesterol and triglycerides between the liver and peripheral tissues.

Following the success of the first edition released five years ago, we would like to introduce this revised second edition of the book entitled *The Biliary System*, a volume in the *Colloquium Series on Integrated Systems Physiology: From Molecule to Function to Disease,* edited by D. Neil Granger and Joey Granger. In this book, the consequences of the complex events involving lipid metabolism in the hepatobiliary system are reviewed with a focus on the translational value of current basic research in health and disease. The teaching aspects of this book are distributed across anatomical aspects of the hepatobiliary system; the physics and chemistry of a complex body fluid such as the bile, as well as the biochemistry of hepatic metabolism of cholesterol and bile acids, including the enterohepatic circulation and the biliary secretion of lipids. Chapters are enriched with multiple figures showing detailed metabolic pathways of lipids, as well as with updated evidence elucidating lipid metabolism in the liver and biliary system, each with authoritative bibliographies.

With the present updated revision, this book is designed to attract the attention of readers by clearly explaining the molecular and cellular pathways that regulate hepatic lipid metabolism and by presenting color figures, tables, and flowcharts that deal with the fundamental mechanisms of lipid synthesis and secretion, bile formation, the enterohepatic circulation, and intestinal absorption of biliary components. In addition, we have added a new Chapter 8, which focuses, from a view point of physical-chemistry and pathophysiology, on the pathogenesis of accelerated cholesterol crystallization and gallstone formation, a very prevalent liver disease worldwide.

The authors are confident that this second edition of *The Biliary System* will help the next generation of students, researchers, scientists, teachers, nurses, and physicians in the field.

David Q.-H. Wang, M.D., Ph.D.
Brent A. Neschwander-Tetri, M.D.
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CHAPTER 1

Introduction

The liver plays a central role in the regulation of cholesterol and bile acid metabolism and is involved in biliary lipid secretion and bile formation. Cholesterol is synthesized from acetyl CoA, and 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase is the rate-limiting enzyme for cholesterol biosynthesis in the body. The liver provides a major source of the cholesterol molecules to the body. Cholesterol biosynthesis is primarily modulated by a negative feedback regulation mechanism through the sterol regulatory element-binding protein isoform 2 (SREBP-2) pathway in the liver. The molecular regulation of SREBPs occurs at two levels—transcriptional and post-transcriptional—in the nucleus of hepatocyte. Cholesterol is secreted into bile either in a "free" (unesterified) form or in its end-product form after it is converted to bile acids by the hepatocytes. Hepatic secretion of biliary cholesterol into the bile is an important pathway for the elimination of cholesterol from the body. Furthermore, cholesterol balance across the liver has a crucial effect on influencing plasma total and LDL cholesterol levels and biliary cholesterol concentrations. Because HMG-CoA reductase catalyzes an irreversible step on the synthesis of mevalonate, it plays an important role in cholesterol biosynthesis in the liver. Also, it is a crucial target for the treatment of hypercholesterolemia or dyslipidemia in patients, as found by basic experiments and confirmed by clinical studies with administration of HMG-CoA reductase inhibitors statins.

The bile acid biosynthesis in the liver involves two major pathways: the "classic" neutral and the "alternative" acidic pathways. In the classic neutral pathway, cholesterol 7α-hydroxylase (CYP7A1) is an important enzyme that is expressed only in the hepatocytes and catalyzes the rate-limiting step in the catabolism of cholesterol to bile acids by converting cholesterol directly into 7α-hydroxycholesterol. In the alternative acidic pathway, cholesterol is transported to mitochondria where it must first be converted into oxysterols by a group of sterol hydroxylases. Bile acid synthesis involves at least 17 enzymes that make 25 possible intermediates. Furthermore, CYP7A1 plays a crucial role in the regulation of bile acid biosynthesis in the liver, which is modulated by a negative feedback regulation system through a group of nuclear receptors. The mechanism underlying the role of farnesoid X receptor (FXR) signaling in the inhibition of *CYP7A1* transcription and bile acid synthesis has been investigated extensively. These studies have revealed that there are two FXR-dependent mechanisms for bile acid inhibition of *CYP7A1* gene transcription. In the liver, FXR can inhibit CYP7A1 via the small heterodimer partner (SHP) pathway. In the intestine, FXR activated

by bile acids stimulates the release of fibroblast growth factor 19 (FGF19). FGF19 circulates to the liver and triggers hepatic FGF receptor 4 (FGFR4) signaling to inhibit CYP7A1. In addition, bile acid inhibition of CYP7A1 is determined, in part, by several FXR-independent mechanisms.

The enterohepatic circulation of bile acids is an important physiological route for recycling of bile acids from the liver to the small intestine and back to the liver. Then, bile acids are re-secreted into bile. The recycling of bile acids plays a vital role in the negative feedback regulation of bile acid biosynthesis in the liver. Furthermore, bile acids not only promote bile flow and intestinal absorption of fat, cholesterol, fat-soluble vitamins, and other nutrients, but also work as signaling molecules and inflammatory agents to regulate lipid, glucose, and energy metabolism by rapidly activating nuclear receptors and cell signaling pathways. Of note, the enterohepatic circulation of bile acids is highly efficient, allowing less than 5% of the secreted bile acids to be lost in the feces. Because biliary bile acids are secreted in such large amounts, approximately 0.4 g of bile acids is lost in the feces per day. Thus, the conversion of cholesterol to bile acids, that is, bile acid synthesis in the liver, can balance the fecal excretion of bile acids, which is also an important route for the elimination of cholesterol from the body.

The bile is produced by the liver and bile formation begins in the bile canaliculi of hepatocytes. On the canalicular membrane of hepatocytes, an ATP-binding cassette (ABC) transporter ABCB11, a bile acid export pump, promotes the secretion of bile acids into bile. Subsequently, biliary bile acids stimulate two other ATP-dependent transporters—ABCB4 and a heterodimer of ABCG5 and ABCG8—to induce the hepatic secretion of phospholipid and cholesterol into bile, respectively. Bile acids are highly soluble in water and are biological detergents. In contrast, cholesterol and phospholipid are virtually insoluble in water. When a critical micellar concentration (CMC) is exceeded, bile acids can self-assemble into simple micelles in bile. Also, they bind with cholesterol and phospholipid to form mixed micelles. These micelles help solubilize cholesterol in bile. Furthermore, the phospholipid molecules can aggregate to form unilamellar vesicles. These vesicles greatly promote the solubilization of cholesterol in bile and help transport the cholesterol molecule from the liver to the small intestine. Although vesicles are quite static structures, the equilibrium between vesicles and micelles is influenced by several factors such as the total lipid concentration and the relative ratio of cholesterol, phospholipids, and bile acids in bile. These physical structures of biliary lipid carriers have an important effect on bile formation, as well as the digestion and absorption of dietary fat, cholesterol, fat-soluble vitamins, and some drugs.

This eBook will carefully review the hepatobiliary aspects of cholesterol and bile acid metabolism and physical-chemistry of biliary lipids, as well as summarize current knowledge of molecular regulation of cholesterol and bile acid biosyntheses in the liver, with emphasis on biliary lipid metabolism that is regulated by nuclear receptors in the hepatobiliary system.

CHAPTER 2

Anatomy of the Liver, Biliary Tract, and Gallbladder

2.1 THE LIVER

2.1.1 Gross and Surface Anatomy

The liver is the largest solid organ in the body. It is wedge-shaped with its base against the right abdominal wall and its tip pointing to the spleen. The liver has two major surfaces: the diaphragmatic and visceral surfaces. The diaphragmatic surface faces anteriorly and superiorly, whereas the visceral surface faces posteroinferiorly. Although most of the liver is covered with a layer of visceral peritoneum, the superior part, called the bare area, is fused to the diaphragm and therefore lacks peritoneum (Figure 2.1). The liver extends from the fifth intercostal space in the right midclavicular line down to the right costal margin, with its size being 12 to 15 cm coronally and 15 to 20 cm transversely. It lies below the diaphragm and occupies most of the right hypochondrial and part of the epigastric regions of the abdomino pelvic cavity. The liver weight ranges from 1.3 to 1.7 kg (between 1.8% and 3.1% of body weight) in most adults, depending on gender and body size. The liver weight in fetuses and children is relatively greater, being 5.6% at 5 months gestational age, 4% to 5% at birth, and 3% at 1 year of age.

The liver is covered by the fibrous "Glisson's" capsule and has a continuous sponge-like parenchymal mass penetrated by tunnels that contain the interdigitating networks of afferent and efferent vessels [1–5]. The primary afferent blood vessels of the liver are the portal vein and hepatic artery. The branches of these vessels within the liver parenchyma are contained together in connective tissue which is contiguous with the mesenchymal components of the liver's mesothelium-covered surface capsule. The finest branches of the efferent vessels become major components of the portal tracts. Other components of the portal tracts include nonparenchymal cells and cell types that make important contribution to liver function, including bile metabolism (cholangiocytes in bile ducts), vascular regulation (sympathetic nerves), pain perception (parasympathetic nerves), immune function (immunocytes), and lymph formation (lymph vessels). The collagenous stroma surrounding the efferent vessel, from the central veins to the hepatic vein, is less robust and contains fewer adventitial cells.

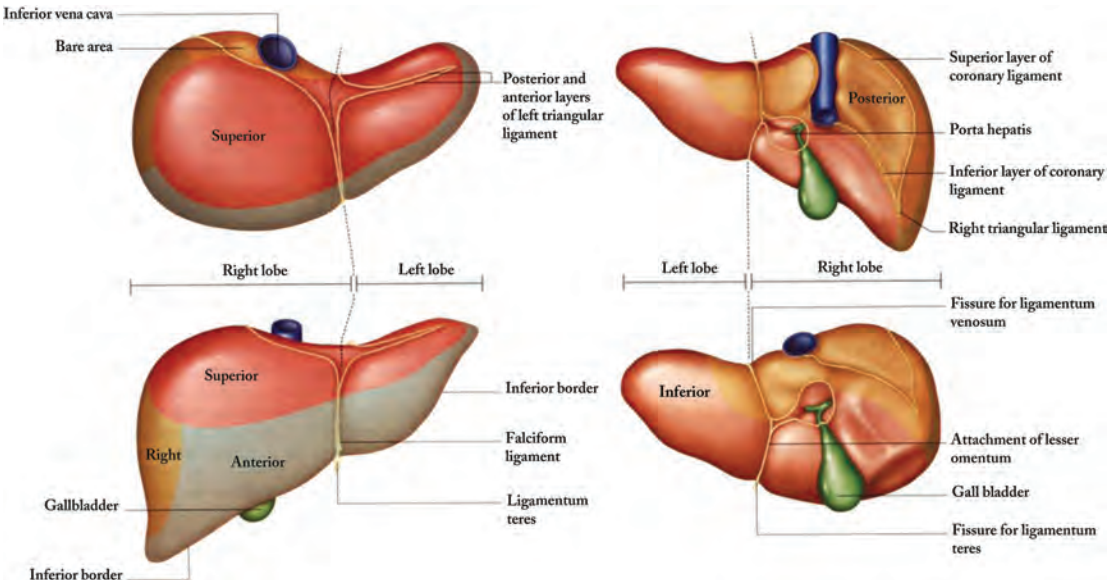

FIGURE 2.1: Gross anatomy of the liver. Top left, superior view; top right, posterior view; bottom left, anterior view; bottom right, inferior view. Used with permission from *Gray's Anatomy: The Anatomical Basis of Clinical Practice*. Editor-in-Chief: Standring S. 39th edition. Elsevier Churchill Livingstone, London, 2005. p. 1214.

At the porta hepatis, defined as the region in which the portal vein and hepatic artery enter the liver and the hepatic bile duct exits the liver, the connective tissue of the capsule is continuous with the fibrous sheath investing the portal vessels and bile ducts and following them to their smallest ramifications [1–5]. At the superior surface of the liver, the capsular peritoneum reflects onto the diaphragm and continues as the parietal peritoneum. The reflections form the coronary ligaments, the right and left triangular ligaments, and the falciform ligament. These ligaments hold the liver in its place and allow the passage of lymphatics, small vessels, and nerves. The falciform ligament, a fold of the parietal peritoneum, extends from the undersurface of the diaphragm between the principal lobes of the liver. The round ligament (ligamentum teres), a fibrous cord containing a remnant of the umbilical vein of the fetus, forms the free border of the falciform ligament. The right and left coronary ligaments are narrow reflections of the parietal peritoneum that suspend the liver from the diaphragm. In addition, there is a large bare area where the liver contacts the diaphragm and retroperitoneum. The vena cava, being retroperitoneal, lies within the bare area and attached to the liver by a ligament or bridge of the liver parenchyma between the caudate and right lobes.

The hepatoduodenal ligament connects the liver to the superior part of the duodenum. It is part of the lesser omentum and sheathes the hepatic artery, the portal vein, bile ducts, nerves, and lymph vessels, all being present within the porta hepatis [6]. In the ligament, the common bile duct lies to the right, the hepatic artery to the left, and the portal vein behind them. Numerous variations in the topography of the hepatic artery are common.

2.1.2 Structural Concepts of Liver Lobes and Segmentation

The human liver is divided into two principal lobes—a large right lobe and a smaller left lobe (Figure 2.2). In general, the falciform ligament on the anterior diaphragmatic surface, and the lesser

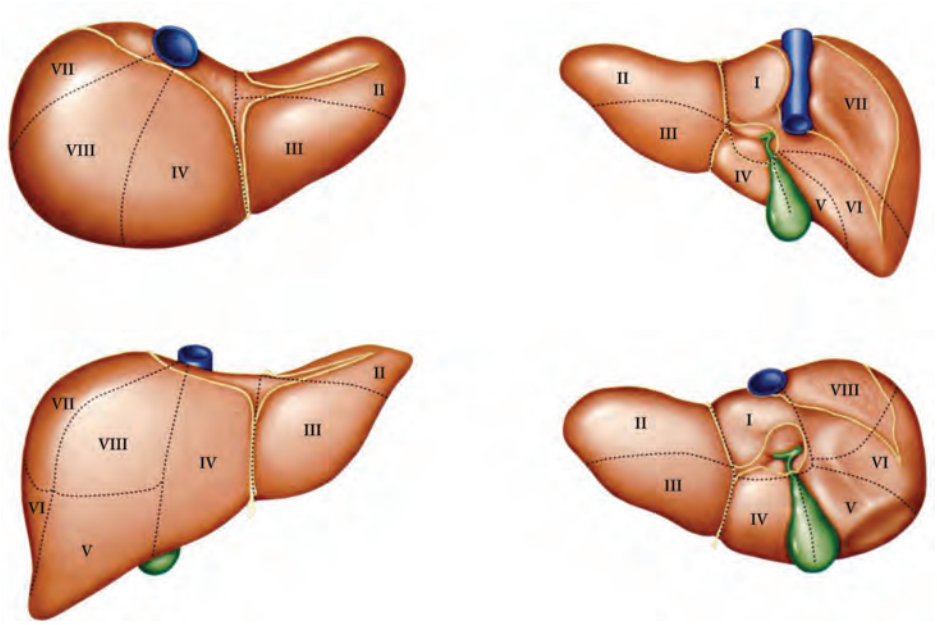

FIGURE 2.2: Segmental anatomy of the liver based on the Couinaud terminology. Eight segments are identified. Top left, superior view; top right, posterior view; bottom left, anterior view; bottom right, inferior view. The segments are sometimes referred to by name—I, caudate (sometimes subdivided into left and right parts); II, lateral inferior; III, lateral inferior; IV, medial (sometimes subdivided into superior and inferior parts); V, anterior inferior; VI, posterior inferior; VII, posterior superior, VIII, anterior superior. Used with permission from *Gray's Anatomy: The Anatomical Basis of Clinical Practice*. Editor-in-Chief: Standring S. 39th edition. Elsevier Churchill Livingstone, London, 2005. p. 1217.

omentum and umbilical fissure on the posterior visceral surface, divide the liver into the conventional right and left lobes [1–5]. However, this division of the liver does not correspond to the division based on branch points in the vascular supply. The liver can be divided on a different plane into right and left livers (or hemilivers), each with its own blood supply and bile duct drainage. The right hemiliver makes up 50% to 70% of the liver mass [1–5]. Two other lobes, the smaller quadrate and caudate lobes, are visible on the visceral surface just to the right of the fissure. Although the right lobe is considered to include an inferior quadrate lobe and a posterior caudate lobe, on the basis of internal morphology (primarily the distribution of blood vessels and nerves), the quadrate and caudate lobes more appropriately belong to the left lobe. Germane to surgical resection, the liver can be further divided into a total of eight segments on the basis of the vascular or bile duct distribution. This segmental nomenclature devised by Couinaud (Figure 2.2) has received the widest acceptance because of its relevance to surgical resection of focal lesions of the liver [7]. This classification is based on the divisions of the portal veins. However, the branching of the portal veins to the left lobe is irregular because of the entry of the umbilical vein, making it desirable to adopt a nomenclature based on the divisions of the arteries or ducts [8].

2.1.3 Large Vessels of the Liver

An important area near the center of the visceral surface is the porta hepatis where most of the major vessels and nerves enter and leave the liver (Figure 2.3). The liver receives blood from two afferent vessels (Figure 2.4). From the portal vein, it obtains nutrient-rich blood containing newly absorbed nutrients, drugs, and possibly microbes and toxins from the gastrointestinal tract. Also, the liver receives oxygen-rich blood from the hepatic artery. Branches of both the portal vein and the hepatic artery carry blood to the liver sinusoids, where many of the nutrients, oxygen, and certain toxic substances are taken up by the hepatocytes. About two thirds of the blood flowing to the liver is from the portal vein while the hepatic artery contributes the other third. In contrast, the hepatic artery supplies about two thirds of the oxygen to the liver while the portal vein delivers the other third after been depleted of much of its oxygen. Metabolic products produced by the hepatocytes and nutrients needed by extrahepatic organs are secreted back into the sinusoids, which then coalesce into the central veins and the blood eventually drains into the hepatic vein.

2.1.3.1 Portal Veins. The portal vein is an afferent nutrient vessel of the liver, which carries blood from the entire capillary system of the gastrointestinal tract, spleen, pancreas, and gallbladder. The portal vein supplies blood to the parenchymal mass through its terminal branches (Figure 2.4).

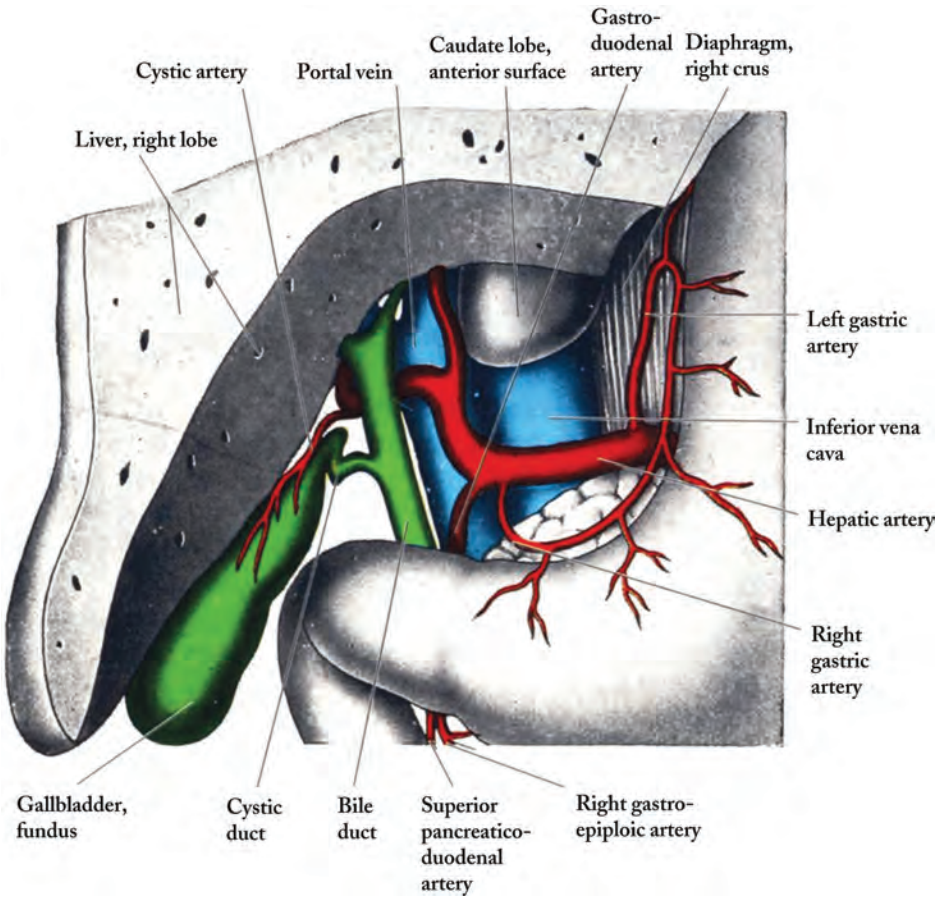

FIGURE 2.3: Anatomy of the porta hepatis, showing the relationship among the common hepatic duct, the cystic duct, the common bile duct, the hepatic artery, and the hepatic portal vein, as well as the Calot's triangle. Used with permission from *Gray's Anatomy: The Anatomical Basis of Clinical Practice*. Editor-in-Chief: Standring S. 39th edition. Elsevier Churchill Livingstone, London, 2005. p. 1218.

The portal vein is formed behind the neck of the pancreas by the confluence of the splenic vein and the superior mesenteric vein. It also receives the superior pancreaticoduodenal vein, the left gastric (coronary) vein, and the cystic vein.

The splenic vein originates from five to six branches that return the blood from the spleen and merge to form a single vessel. The superior mesenteric vein carries blood from the small intestine, ascending colon, and transverse colon. The inferior mesenteric vein returns blood from the area drained by the superior and the inferior left colic and the superior rectal veins.

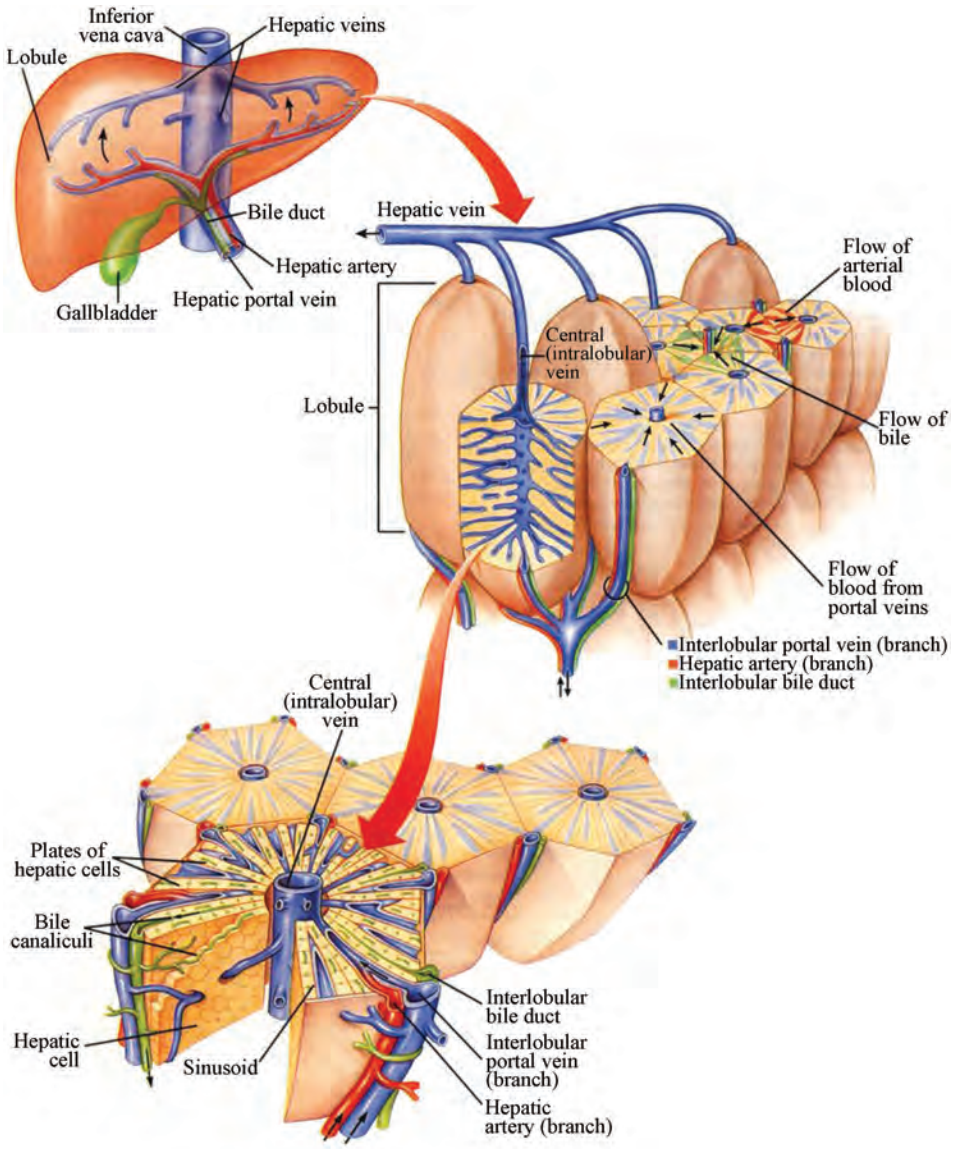

FIGURE 2.4: Microscopic structure of the liver. Top panel shows the location of liver lobules relative to the overall circulatory scheme of the liver. Middle and bottom panels show enlarged views of several lobules. Blood from the hepatic portal veins and hepatic arteries flows through sinusoids and thus past plates of hepatic cells toward a central vein in each lobule. Bile secreted by the hepatocytes flows through bile cannaliculi toward hepatic ducts that eventually drain the bile from the liver. Used with permission from *Anatomy & Physiology*. Editors: Thibodeau GA and Patton KT. 4th Edition. Mosby. St. Louis. 1999. p. 752.

The portal trunk runs in the hepatoduodenal ligament in a plane dorsal to the bile duct and the hepatic artery and splits into two lobar veins before entering the portal fissure (Figure 2.4). The right lobar vein, short and thick, receives the cystic vein. The left lobar vein, longer and smaller, is joined by the umbilical vein and the paraumbilical veins.

2.1.3.2 Hepatic Arteries. The common hepatic artery is the second major branch of the celiac axis. It splits into the right and the left hepatic arteries to supply the corresponding hemilivers (Figure 2.4). The right and the left hepatic arteries each divide into two arteries that supply the right anterior and posterior sections and the left medial and lateral sections, respectively. The middle hepatic artery arises from the right or left hepatic artery and supplies the quadrate lobe [9]. The blood of hepatic artery flow provides oxygen and nutrients to the tissues of portal tracts, the liver capsule, and the walls of large vessels. In portal tracts, arterial branches form a capillary network arborized around bile ducts. Although arterial and portal blood appear to be well mixed before entering sinusoids, the direct supply of arterial blood to sinusoids by small branches of the hepatic artery remains unknown.

2.1.3.3 Hepatic Veins. There are three main hepatic veins (Figure 2.4). The middle and left veins unite before entering the vena cava in 65% to 85% of individuals. In 18% of individuals, there are two right hepatic veins draining into the vena cava. In another 23%, there is a separate middle or inferior right hepatic vein draining segments V or VI, respectively. A small amount of venous drainage from the liver surrounding the cava drains directly into the cava via small veins.

2.1.4 Lymphatic Drainage

The formation of hepatic lymph is poorly understood yet overproduction of hepatic lymph is responsible for the development of ascites in the setting of obstruction of sinusoidal blood flow. Lymphatic vessels can be identified in portal triads and these likely receive lymph from the space of Disse that exists between the fenestrated sinusoidal endothelial cells and the adjacent hepatocytes. A mechanism responsible for the countercurrent flow of lymph in spaces of Disse and flow of blood in sinusoids other than simple hydrostatic pressure remains unknown. A large volume of lymph (approximately more than 50% of all lymph) is produced in the liver. Lymphatic vessels from the gallbladder and cystic duct drain principally into the hepatic nodes via the cystic duct node, a constant lymph node located at the junction of the cystic duct and common hepatic duct [1–5]. Lymphatic vessels from the hepatic ducts and upper common bile duct drain into the hepatic lymph

nodes, a chain of lymph nodes that follows the course of the hepatic artery to drain into the celiac lymph nodes. Lymph from the lower bile duct drains into the lower hepatic nodes and the upper pancreatic lymph nodes.

2.2 THE BILIARY TRACT AND GALLBLADDER

The path by which bile flows from the liver to the duodenum is as follows: bile secreted by the hepatocytes passes through canaliculi between hepatocytes to the center of the acinus, which is also the periphery of the lobule, to join small bile ducts (Figure 2.5). The small bile ducts within the right and left lobes of the liver join to form two larger ducts that emerge from the undersurface of

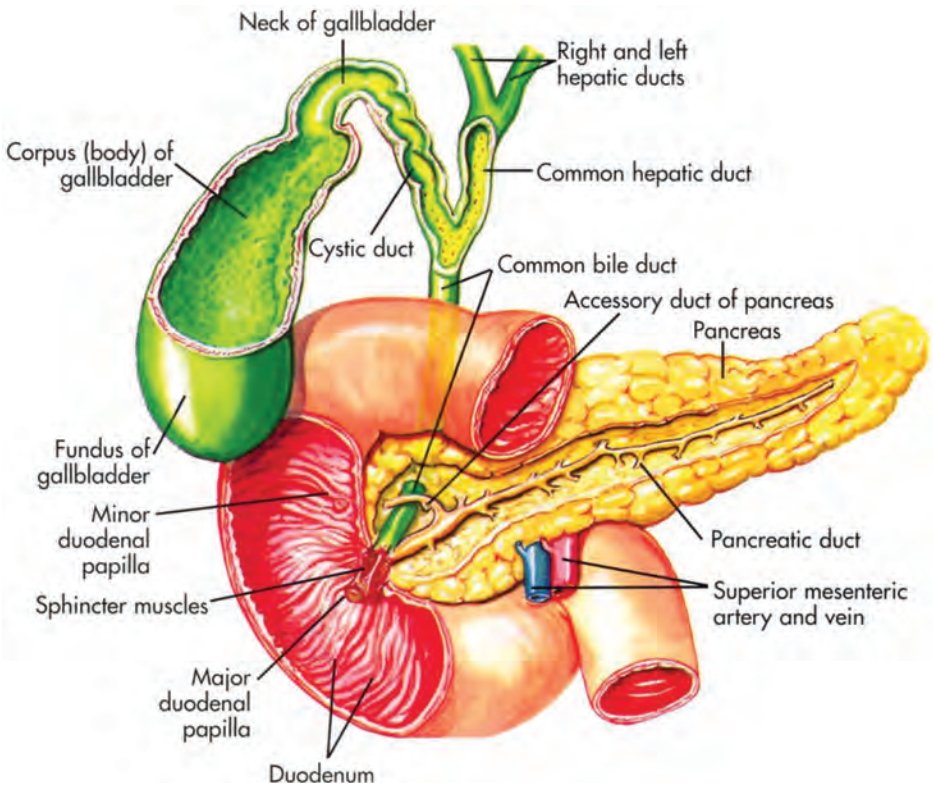

FIGURE 2.5: Common bile duct and its tributaries. Used with permission from *Anatomy & Physiology*. Editors: Thibodeau GA and Patton KT. 4th Edition. Mosby. St. Louis. 1999. p. 754.

the liver as the right and left hepatic ducts [1–4]. These two bile ducts immediately join to form one bile duct called the common hepatic duct. The common hepatic duct merges with the cystic duct from the gallbladder to form the common bile duct [10–15]. The latter opens into the descending part of duodenum called the major duodenal papilla (of Vater) [16]. This papilla is located 7 to 10 cm below the pyloric opening from the stomach. In general, the biliary tract is divided into three parts: the intrahepatic bile ducts, the extrahepatic bile ducts, and the gallbladder.

2.2.1 Intrahepatic Bile Ducts

The biliary drainage of the right and left lobes of liver is into the right and left intrahepatic bile ducts, respectively. The right hepatic duct is formed from the unification of the right posterior and right anterior segmental ducts. The left hepatic duct is formed by the unification of the three segmental ducts draining in the left side of the liver. The left hepatic duct crosses the base of segment IV in a horizontal direction to join the right hepatic duct and form the common hepatic duct.

2.2.2 Extrahepatic Bile Ducts

The right and left hepatic ducts often unite just outside of the liver parenchyma to form the common hepatic duct (Figure 2.5). The common hepatic duct is a segment of bile duct between the junction of the right and left hepatic ducts and the entrance of the cystic duct emanating from the gallbladder, and its length is variable. The common bile duct is formed by the unification of the cystic duct and the common hepatic duct. Its average length is approximately 8 cm, which can vary depending on the point of union of the cystic duct and the common hepatic duct. Generally, the diameter of the common bile duct varies from 4 to 7 mm. If its diameter exceeds 7.5 mm, the common bile duct is considered distended.

The relationship between the distal common bile duct and pancreatic duct is variable (Figure 2.6). In most instances (90%), the common bile duct and pancreatic duct join to form the common channel, which is less than 1.0 cm in length and is called the ampulla (meaning “jug”). In rare situations (10%), these two structures may unite outside the duodenal wall to form a longer than 1.0 cm common channel, or alternatively the biliary and pancreatic ducts can drain separately into the duodenum [6, 17].

The sphincter of Oddi is usually considered to be composed of the lower portion of the common bile duct and the terminal portion of the pancreatic duct (Figure 2.6). The sphincter mechanism functions independently from the surrounding duodenal musculature and has separate sphincters for the distal bile duct, the pancreatic duct, and the ampulla. The entire sphincter

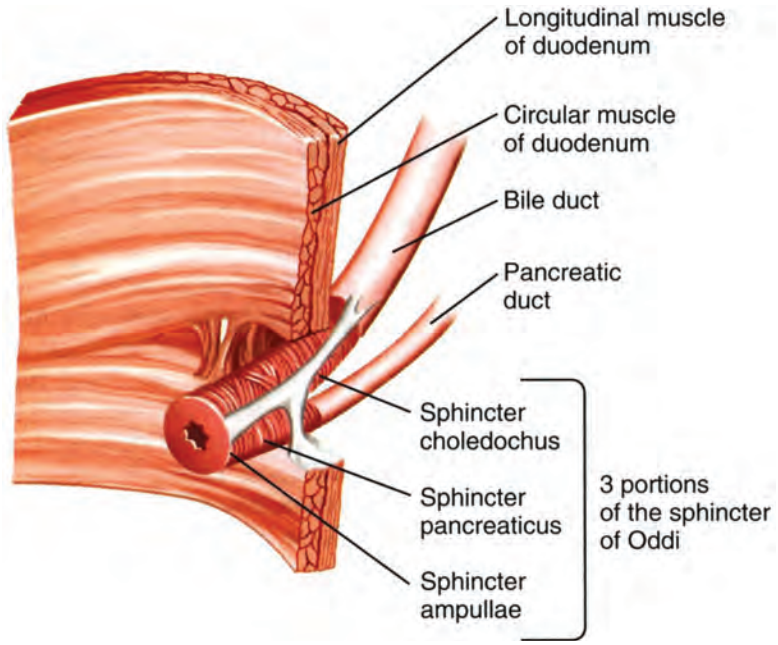

FIGURE 2.6: Anatomy of the sphincter of Oddi. This diagram shows the three portions of the sphincter of Oddi: the sphincter ampullae (surrounding the short common channel), the sphincter pancreaticus, and the sphincter choledochus (the largest portion). Used with permission from Elmunzer BJ and Elta GH. Biliary Tract Motor Function and Dysfunction in *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. Editors: Feldman M, Brandt L, and Friedman L. the 9th Edition. Elsevier Saunders. 2010; p. 1068.

mechanism is actually composed of four sphincters containing both circular and longitudinal smooth muscle fibers, that is, the superior and the inferior sphincter choledochus, the sphincter pancreaticus, and the sphincter of the ampulla.

2.2.3 Gallbladder

The gallbladder is a pear-shaped organ located on the inferior surface of the liver at the junction of the right and left hepatic lobes, which typically hangs from the anterior inferior margin of the liver. It is found on the right side just deep to where the lateral margin of the rectus abdominis muscle crosses the costal margin of the rib cage. In general, the size of gallbladder varies between 7 and 10 cm in length and between 2.5 and 3.5 cm in width. The volume of a moderately distended

gallbladder is approximately between 30 and 60 mL. Furthermore, the gallbladder's volume varies considerably, being large because of the storage of concentrated bile in the fast state and becoming small after its postprandial emptying [18]. The gallbladder can be divided into four parts: the neck, body, infundibulum, and fundus (Figure 2.5). The neck of gallbladder connects the cystic duct in a cephalad and dorsal direction. The cystic duct often joins the lateral aspect of the supraduodenal portion of the common hepatic duct to form the common bile duct. The length of the cystic duct varies from 2 to 4 cm. The cystic duct may irregularly join the right hepatic duct or extend downward to connect the retroduodenal bile duct. The body is the central part of the gallbladder. The fundus projects downward beyond the inferior border of the liver. Hartmann's pouch is an asymmetrical bulge of the infundibulum close to the gallbladder's neck. Calot's triangle is formed by the common hepatic duct medially, the cystic duct laterally, and the cystic artery superiorly [19]. During cholecystectomy, a clear visualization of Calot's triangle is necessary for a correct identification of all structures within this triangle (Figure 2.3). In most cases, the cystic artery arises as a branch of the right hepatic artery within this triangle.

2.3 LIVER, GALLBLADDER, AND BILE DUCT CELL TYPES

2.3.1 Parenchymal Cells

2.3.1.1 Hepatocytes. The microscopic architecture of the liver has been divided into functional units called lobules based around central veins or acini based around portal triads (Figure 2.7). The hepatocytes of the portal based acinus are further subdivided into zone 1 hepatocytes that are closest to the portal triad and are the first to receive nutrient rich and well oxygenated blood, zone 3 hepatocytes which are most distal from the portal triads and zone 2 hepatocytes in between. The acinar structure has functional significance since zone 1 hepatocytes exhibit significant functional differences from zone 3 hepatocytes based on their respective roles in metabolism. The lobule is more of an anatomical concept with less functional significance. Between the portal triads bringing blood into the liver and the central veins are the hepatocytes that are arranged in irregular, branching, interconnected plates around the central vein (Figure 2.8). Hepatocytes are large polyhedral cells and account for approximately 70% of cells within the liver. Their cell sizes vary from 20 to 30 μm in diameter. Hepatocytes are polarized epithelial cells and their plasma membranes have three distinct domains: (i) the basolateral sinusoidal surface (about 37% of the cell surface) being in direct contact with plasma via the fenestrae of the specialized hepatic sinusoidal endothelial cells; (ii) the apical canalicular surface (about 13% of the cell surface) enclosing the entire bile canaliculus; and (iii) contiguous lateral surfaces

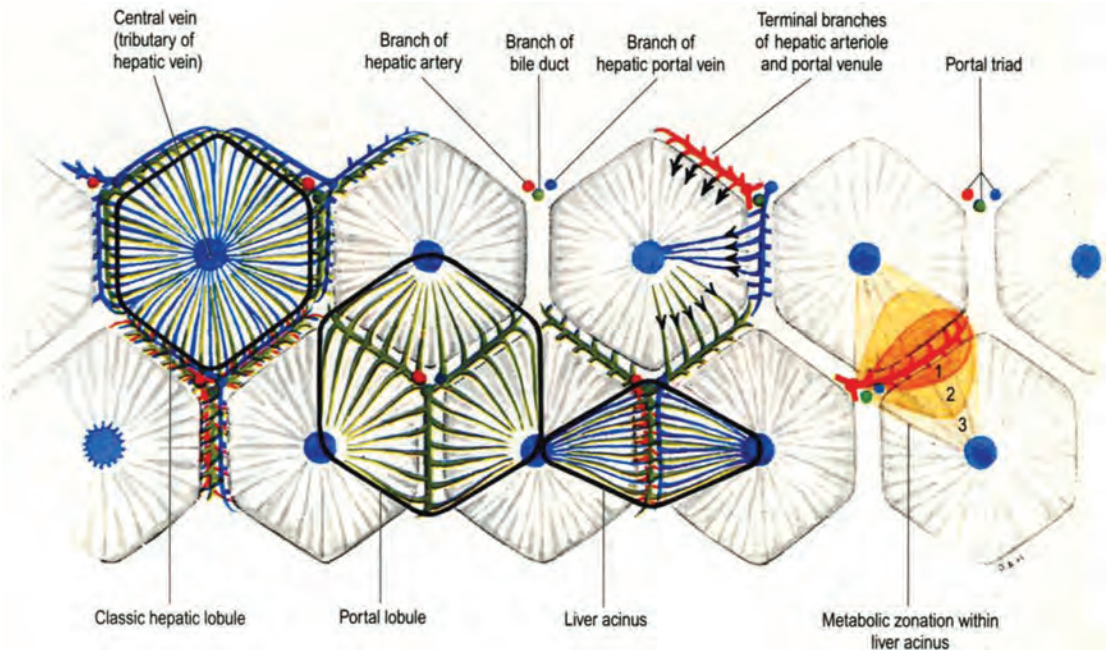

FIGURE 2.7: The histological organization of the liver. This diagram shows the principal types of subdivisions. Although the classic hepatic lobules are shown as regular hexagons, their real appearance is highly variable. The portal lobule, centered on the portal triad and biliary drainage is also shown. Used with permission from *Gray's Anatomy: The Anatomical Basis of Clinical Practice*. Editor-in-Chief: Standring S. 39th edition. Elsevier Churchill Livingstone, London, 2005. p. 1222.

(about half of the cell surface) adjacent to other hepatocytes. The sinusoidal and canalicular surfaces contain a large number of microvilli, which significantly enlarge the surface area of these domains. The space between the endothelia and the sinusoidal villi is termed the space of Disse, which provides room for the bidirectional exchange of water and solutes between the plasma and hepatocytes at the sinusoidal surface. There are many transporter proteins located on the basolateral membrane for the molecular transfer of solutes, which promote facilitated diffusion or energy-consuming active transport. The canalicular domains of two adjacent hepatocytes are sealed at the periphery by tight junctions and form the bile canaliculus, which is the beginning of the biliary drainage system.

2.3.2 Sinusoidal Nonparenchymal Cells

Cells within the liver that are not hepatocytes are collectively called nonparenchymal cells. This is a diverse population serving a wide variety of metabolic, immune and structural functions.

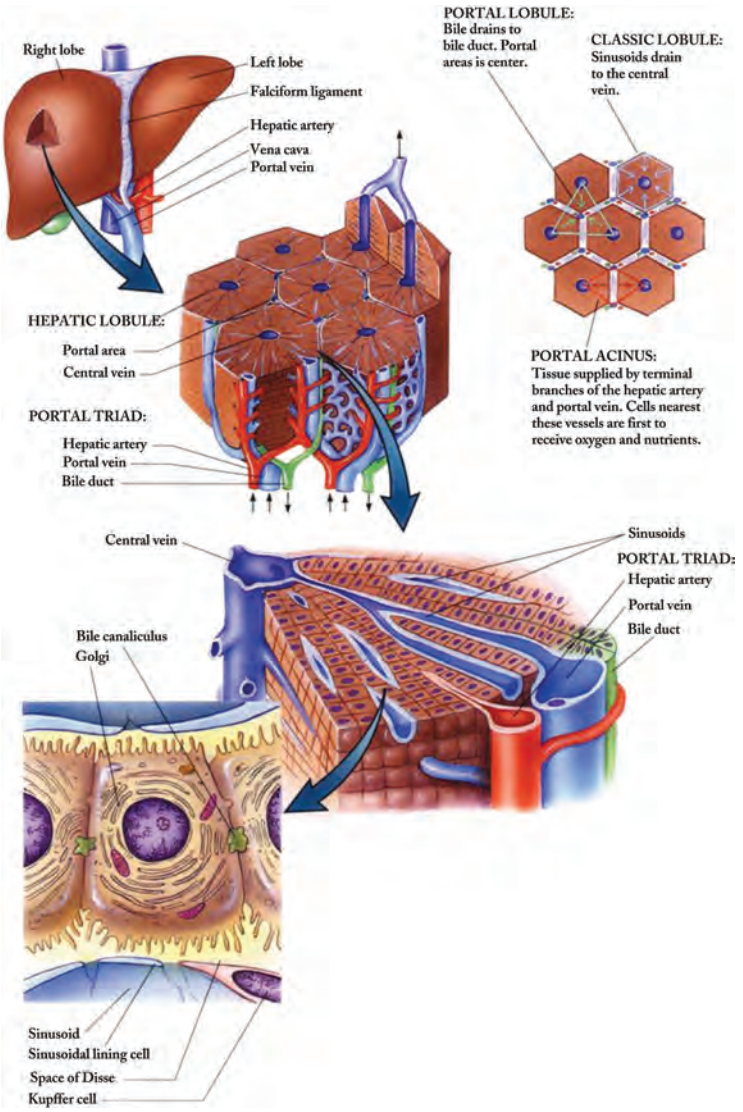

FIGURE 2.8: Microscopic anatomy of the liver. Left top panel shows schematic three-dimensional representation of a liver lobule. Right bottom panel shows enlarged view of a small part of a liver lobule. The directions of blood flow and bile flow are indicated by arrows; however, their directions are opposite. Used with permission from *Color Atlas of Histology*. Editors: Gartner LP and Hiatt JL. 3rd edition. Lippincott Williams & Wilkins, Philadelphia, 2000. p. 301.