Chapter 1
Biliary System Anatomy, Physiology, and Embryology

Cecilia G. Ethun and Shishir K. Maithel

Overview

The biliary system is equally complex and fascinating. From inception, its development, structure, and function rely heavily on other organ systems, yet it maintains a degree of independence and unique properties found nowhere else in the body. When operating on the biliary tract, thorough knowledge of this organ system is of critical importance. Never is this more apparent than when faced with aberrance and injury. However, by strengthening our understanding of biliary embryology, anatomy, and physiology, we can better prepare and manage when things go awry.

Embryology

Overview

The embryologic development of the biliary tract is closely associated with, and largely dependent upon, that of the liver. To start, both are derived from embryonic endoderm. What follows is a series of intricate signaling pathways within and among these growing cell populations and their environment that, in turn, come to form the hepatobiliary system.

C.G. Ethun, M.D. • S.K. Maithel, M.D., F.A.C.S. (✉)
Division of Surgical Oncology, Department of Surgery, Winship Cancer Institute, Emory University, Atlanta, GA, USA
e-mail: smaithe@emory.edu

E. Dixon et al. (eds.), *Management of Benign Biliary Stenosis and Injury*, DOI 10.1007/978-3-319-22273-8_1

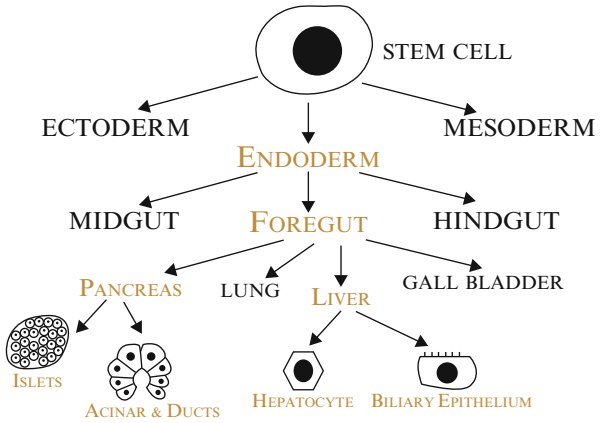

Fig. 1.1 Cell lineage schematic for hepatic, pancreatic, and biliary development from a multipotent progenitor stem cell. El-Gohary Y, Gittes GK. Embryologic development of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1A.1. p. 19

Around the middle of the third week of gestation, the liver primordium appears as an endodermal outgrowth at the distal end of the foregut. The liver bud invades the surrounding mesenchyme of the septum transversum cranially and begins a period of rapid proliferation and branching, giving rise to liver parenchyma and the intrahepatic biliary tree. As the liver primordium grows caudally, the connection between the liver and the foregut narrows to form the bile duct. The gallbladder and cystic duct develop from a ventral outgrowth of the bile duct. As the duodenum rotates to the right and becomes C-shaped around the sixth week of gestation, the ventral pancreatic bud that had initially developed at the base of the liver bud swings posteriorly, taking with it the distal segment of the bile duct. The hepatoblasts eventually differentiate into hepatocytes and cholangiocytes, and by the twelfth week, bile produced in the liver begins draining down the newly formed ductal system [1] (Fig. 1.1).

Endodermal Patterning

Derived from the endodermal germ layer, the primitive gut tube is divided into the foregut, midgut, and hindgut. Within each of these domains are specialized regions. The fates of these regions are determined by the expression of specific transcription factors followed by a series of reciprocal interactions between the endoderm and surrounding mesoderm, known as *endodermal patterning*. This complex web of positive and negative signaling appears to be critical for the specialization of the anterior foregut endoderm for organs such as the liver and ventral pancreas, and posterior foregut endoderm for the intestine and dorsal pancreas [2, 3].

Hepatic Competence

Before hepatic specification can occur, the primitive foregut endoderm must first have the potential to adopt its hepatic fate. This inherent ability of the endoderm to begin the process of hepatogenesis, known as *hepatic competence*, is thought to be mediated through transcription factors, such as the HNF-3/fork head and GATA-4 transcription factor families. It is proposed that HNF-3 binding to DNA modulates the chromatin structure in such a way that allows for other binding regions essential for liver bud initiation to become available [4, 5]. One such region within the albumin enhancer is bound by the GATA-4 transcription factor, and is essential for its enhancer activity [6]. Through en vivo footprinting, it has been suggested that HNF-3 and GATA-4 function cooperatively to prime the foregut endoderm to move toward hepatic gene expression, thus making it competent for *hepatic specification* [5, 7].

Liver Specification

Although little is known about the in vivo pathways, several in vitro signaling pathways have been implicated in hepatic specification of the foregut. Hematopoietically expressed homeobox gene (*HHEX*) is one of the earliest foregut markers and is essential for normal liver development in mice [8, 9]. However, expression of *HHEX* alone does not ensure proper liver bud initiation. β-catenin is normally expressed in posterior endoderm and is integral in hindgut development. When activated in the anterior endoderm, β-catenin directly targets and downregulates *HHEX* expression, leading to inhibition of liver formation. Thus, both the expression of *HHEX* and the specific inhibition of β-catenin are necessary to facilitate liver bud development [10]. *FGF4* and *WNT* similarly promote hindgut formation in the posterior endoderm and are inhibited in the anterior endoderm to allow liver development [10]. *FGF2* and bone morphogenetic proteins (BMPs) from the cardiogenic mesoderm and septum transversum mesenchyme, respectively, have also been implicated in liver specification and development, though their exact function and interaction with the endoderm is not entirely understood [11, 12].

Hepatic Bud Morphogenesis and Growth

Once hepatic specification is complete, the anterior endoderm starts the process of hepatic bud morphogenesis (Fig. 1.2a). Mediated by the transcription factor HHEX, growth begins with the transformation of hepatoblasts from simple columnar cells to pseudostratified epithelium, resulting in thickening of the hepatic endoderm region [13]. The laminin- and collagen IV-rich basal membrane layer surrounding the hepatic endoderm then degrades, allowing hepatoblasts organized in cords to begin their invasion of the septum transversum mesenchyme (Fig. 1.2b). This degradation of the basal lamina and subsequent migration of hepatoblasts is thought to

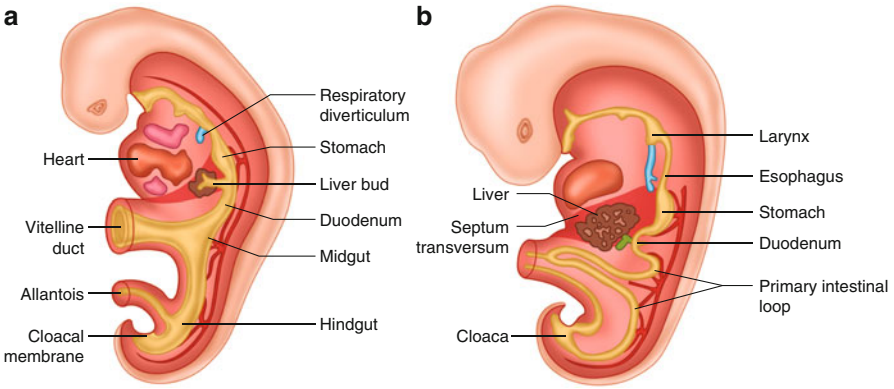

Fig. 1.2 (**a**) A 3-mm embryo (~25 days) showing the primitive gastrointestinal tract and formation of the liver bud. The bud is formed by endoderm lining the foregut. (**b**) A 5-mm embryo (~32 days). Epithelial liver cords penetrate the mesenchyme of the septum transversum. Sadler TW. Langman's Medical Embryology. 11th ed. Philadelphia: Lippincott, Williams & Wilkins; 2010. Figure 14.14. p. 217

be controlled by the transcription factors PROX1 (prospero-related homeobox) and ONECUT1 and -2 [14, 15]. In addition to transcription factors, the extracellular matrix environment and its interaction with hepatoblasts have also been shown to play an important role in this process. These include extracellular matrix remodeling enzymes (matrix metalloproteinases) as well as extracellular matrix protein receptors (β1-integrins) [16, 17].

As liver development within the septum transversum continues, epithelial-mesenchymal interactions, regulated by several growth factors and signals, remain critical for proper organogenesis. One such factor is hepatocyte growth factor (Hgf), which is produced by the mesenchymal cells lining the sinusoids and interacts with hepatocytes via the c-Met tyrosine kinase receptor. Mutations in Hgf have been shown to cause hepatocyte apoptosis, leading to severe liver hypoplasia [18]. Mutations in *HLX* homeobox gene and *BMP4*, which are expressed in septum transversum mesenchyme, and SMAD2 and -3 proteins of the TGF-β signaling pathway similarly result in severe liver hypoplasia [11, 19, 20].

Biliary Morphogenesis

Around the fifth week of gestation, morphogenesis of the biliary tract begins. This process can be broken down into five distinct steps based on observed histology and immunohistochemistry. First, hepatoblasts near the portal mesenchyme express an overabundance of biliary-specific genes, signaling their fate as biliary epithelium.

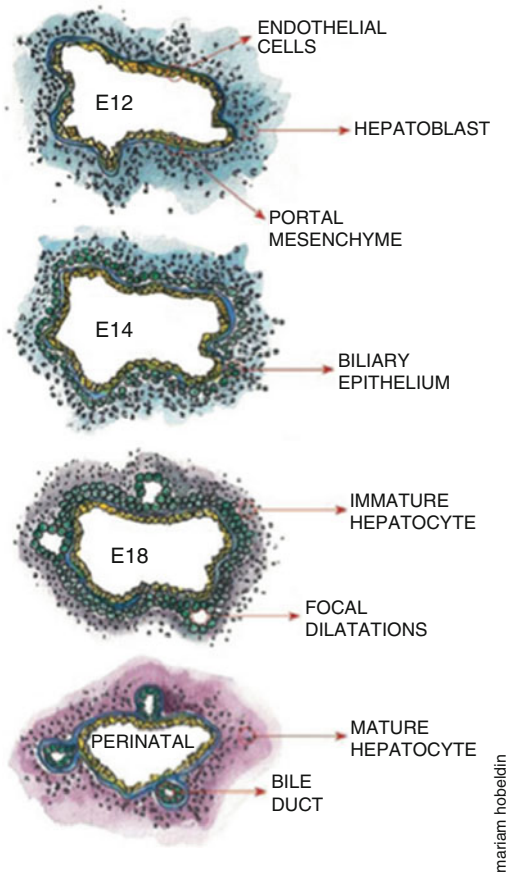

Fig. 1.3 Overview of intrahepatic bile duct formation around the portal vein. Hepatoblasts in the portal mesenchyme vicinity begin to acquire the biliary epithelial cell marker (KRT19) and downregulate hepatic genes, first forming a single layer, then a bilayer with focal dilations that eventually form the intrahepatic bile ducts. The rest of the bilayer regresses. El-Gohary Y, Gittes GK. Embryologic development of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1A.5. p. 24

In the second step, these biliary precursor cells form a single layer around the portal mesenchyme, known as the ductal plate, followed by the formation of a second layer in the third step. The fourth step is marked by significant remodeling of the ductal plate, in which focal dilatations form between the two cell layers giving rise to the bile ducts, while those cells not involved in duct formation regress. The final step begins after birth and involves the incorporation of the bile ducts into the portal mesenchyme [21] (Fig. 1.3).

Hepatoblast Differentiation

While the origin of the biliary ductal system has been subject to much debate, the prevailing theory is that biliary epithelium stems from biopotential hepatoblasts capable of developing into either hepatocytes or cholangiocytes [22] (Fig. 1.1). This is supported largely by the observation that nearly all early hepatoblasts express markers for both hepatocytes (*ALB*) and biliary epithelial cells (*KRT19*) [23]. Thus,

as hepatoblasts differentiate, their expression of these genes varies depending on their fate, such that biliary epithelial cells upregulate biliary-specific *KRT19* while downregulating liver-specific genes. This theory of biopotential progenitor cells is further supported by transplantation studies, in which fetal liver fragments transplanted before the development of intrahepatic bile ducts into the testes of syngeneic animals still gave rise to both hepatocytes and normal bile ducts [24].

Biliary Epithelial Cells and Formation of the Ductal Plate

The exact mechanisms by which hepatoblasts differentiate into biliary epithelial cells are not well understood, though several factors have been implicated. The ONECUT protein hepatocyte nuclear factor (HNF)-6 has been identified as the first transcription factor required for the initiation of biliary epithelial cell differentiation and is additionally thought to confine biliary differentiation to the areas surrounding the portal mesenchyme and restrict the number of cells involved [21, 25]. Normally expressed in the biliary epithelial cells of the intrahepatic bile ducts, primordial gallbladder, extrahepatic bile ducts, and in hepatoblasts, *HNF6*−/− embryo develops severe biliary anomalies, characterized by an absent gallbladder, an enlarged structure connecting the liver with the gallbladder in place of the extrahepatic bile duct, and cholestasis due to large intrahepatic cystic formations. These abnormal cysts are similar to those seen in Caroli disease, though no direct correlation has been identified [25].

Interactions between cells and the surrounding mesenchyme are also thought to be important for biliary epithelial cell differentiation [21]. This role of the mesenchyme can be demonstrated by examining FOXF1, a transcription factor found in gallbladder mesenchyme. *FOXF1*+/− mice were found to have significant structural abnormalities of the gallbladder, a reduced mesenchyme, an absent biliary epithelial cell layer, and deficient external smooth muscle. Interestingly, because it is not found in intrahepatic biliary duct mesenchyme, *FOXF1*+/− mice were spared from intrahepatic ductal abnormalities [26]. Components of the extracellular matrix of the portal mesenchyme, namely laminin, fibronectin, and collagen I and IV, are also implicated in biliary cell differentiation, as are specialized laminin receptors composed of biliary-specific integrin heterodimers found exclusively on ductal plate cells [27–31].

Ductal Plate Remodeling

Remodeling of the ductal plate occurs through the formation of focal dilatations in the ductal bilayer surrounding the portal vein (Fig. 1.3). Those cells not involved in bile duct formation regress through apoptosis [32]. Though this process of remodeling is not entirely understood, cell-cell and cell-matrix interactions, as well as soluble factors, are thought to play a role. The balance between β-catenin, whose expression increases during remodeling, and E-cadherin, whose expression decreases, is one example of a cell-cell interaction that may be necessary to control

the remodeling phase of the ductal plate [33]. Tenascin, a component of the extracellular matrix found specifically at the interface between the mesenchyme and the ductal plate cells of migrating tubules and hilar ducts, but not peripheral ones, is thought to contribute to duct morphogenesis through time- and site-specific cell-matrix interactions [21, 29].

Biliary Tubulogenesis

Once ductal plate remodeling is underway, biliary tubulogenesis begins via cholangiocyte proliferation. There is some evidence in in vitro studies that suggests soluble factors may drive biliary tubule formation, as demonstrated when co-cultured biliary epithelial cells and hepatocytes induced duct morphogenesis, leading to well-formed, luminal bile ducts. This phenomenon was then reproduced when new biliary epithelial cells were grown in the conditioned, previously co-cultured medium [34]. Furthermore, studies focusing on biliary inflammatory processes and oncogenesis have shown that certain factors, such as insulin-like growth factor-1 (IGF-1), interleukin-6 (IL-6), and vascular endothelial growth factor (VEGF), may stimulate cholangiocyte proliferation [35, 36]. Their role in normal human fetal tubulogenesis, however, is unclear.

Extrahepatic Biliary Tract

Little is known about the morphogenesis of the extrahepatic biliary tract. It is believed that prior to expansion, the liver primordium develops into two portions: the cranial, which will invade the septum transversum mesenchyme to become the liver parenchyma and intrahepatic bile ducts, and the caudal portion, which will become the extrahepatic bile duct [22]. However, neither the distinction between the cranial and caudal portions nor their degree of interaction or overlap is well understood. Still, observational studies have shown that mice deficient in pancreatic and duodenal homeobox-1 (*PDX1*), *HNF6*, *HNF1β*, or *FOXF1*, demonstrate significant gallbladder and common bile duct malformations, suggesting their role in the development of the extrahepatic biliary system [25, 26, 37, 38].

Anatomy

Overview

The biliary tract and its supporting cast of arteries, veins, lymphatics, and nerves are highly anatomically variable, with aberrant biliary anatomy seen in roughly 30–40 % of patients and in up to two-thirds when vascular variations are considered [39–41]. Surgery involving the biliary tract requires good exposure and meticulous

dissection, and injury to the tract and its surrounding structures can be devastating. Thus, detailed knowledge of biliary anatomy, including the common variants and anomalies, is essential to operate safely and successfully on this organ system.

Intrahepatic Biliary Anatomy

The anatomy of the intrahepatic bile ducts is closely associated with that of the liver. The segmental anatomy of the liver is determined by the portal venous system, as it bifurcates at the hilum and branches within the liver parenchyma. Based on Couinaud's classification, this includes segment I, which is the caudate lobe, segments II, III, and IV, which comprise the left hemiliver, and segments V, VI, VII, and VIII, which comprise the right hemiliver [42, 43]. Running roughly parallel with the portal veins are the corresponding hepatic arteries and bile ducts, which together form the portal triads. Smaller intrahepatic duct tributaries drain the hepatic segments and converge to create the left and right hepatic ducts within their respective hemilivers.

The left hepatic duct drains the left liver, and is composed of ducts draining segments II, III, and IV. The duct draining segment III is relatively large and is joined by a smaller segment II duct, whose course runs obliquely toward the porta hepatis. In the vast majority of patients, their union is found behind the left portal vein at, or slightly left of, the umbilical fissure, although in 16 % it may be found to the right [44]. The segment IV duct, comprised of tributaries from IVa (superior) and IVb (inferior), then joins to form the left hepatic duct, as it courses at the base of segment IV just superior and posterior to the left branch of the portal vein (Fig. 1.4). This classic distribution of the left intrahepatic biliary ductal system, however, exists in only 60–67 % of patients, with variations characterized by the insertion of the segment IV duct [44, 45]. The most common variant is the insertion of the segment IV duct into segment III, prior to its union with the duct from segment II, which is seen in roughly 25 % of patients. In 3–10 %, the tributaries from segments IVa and IVb insert independently, and in 2 % the duct from segment IV joins the common hepatic duct [44] (Fig. 1.5d).

The right hepatic duct drains the right liver and arises from the union of two main sectoral ducts—the right anterior and right posterior—each accompanied by their corresponding portal venous pedicles. Taking a nearly horizontal course, the right posterior sectoral duct is formed by the confluence of the ducts draining segments VI and VII. The shorter and more vertical right anterior sectoral duct is formed by the ducts of segments V and VIII. Variations in segmental drainage of the right intrahepatic ductal system are more common than in the left and primarily involve aberrant ducts from segments VIII (20 %), VI (14 %), and V (9 %) (Fig. 1.5a–c). As it approaches the hilum, the right posterior sectoral duct wraps around superiorly to the right anterior pedicle and drains into the right anterior sectoral duct just above the right branch of the portal vein [44]. However, roughly 20 % of individuals have a right posterior duct that drains inferiorly to the right anterior pedicle, and up to 43 % have entirely independent drainage of the right anterior and right posterior sec-

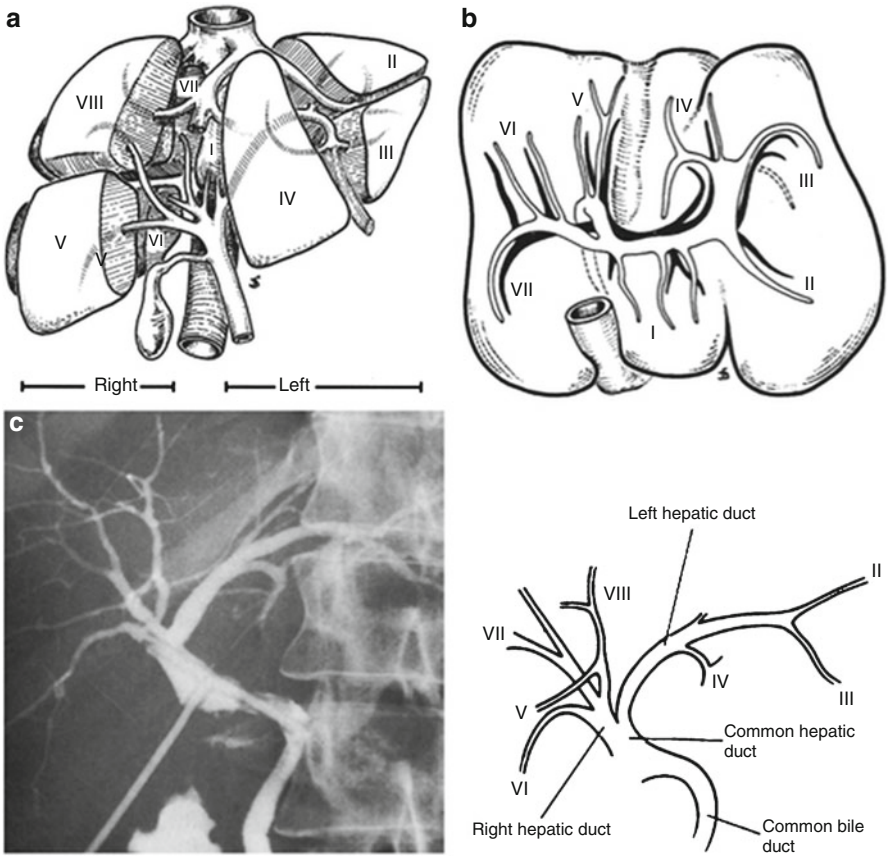

Fig. 1.4 (**a**) Biliary drainage of the two functional hemilivers. Note the position of the right anterior and right posterior sectors. The caudate lobe drains into the right and left ductal system. (**b**) Inferior aspect of the liver. The biliary tract is represented in *black*, and the portal branches are represented in *white*. Note the biliary drainage of segment IV (segment VIII is not represented because of its cephalad location). (**c**) T-tube cholangiogram shows the most common arrangement of hepatic ducts. Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1B.15. p. 39

toral ducts, which are seen in a variety of extrahepatic configurations, without a common right hepatic duct [45, 46].

The caudate lobe (segment I) has its own biliary drainage and can be divided into three parts—right and left portions, and a caudate process. In 44 % of cases, three separate ducts drain these three parts, while in 26 % the right portion and caudate process share a common duct. In the vast majority of individuals (78 %), the ductal tributaries from the caudate lobe drain into both the left and right hepatic ducts, although exclusive drainage into either the left (15 %) or the right (7 %) hepatic ductal system does occur [45].

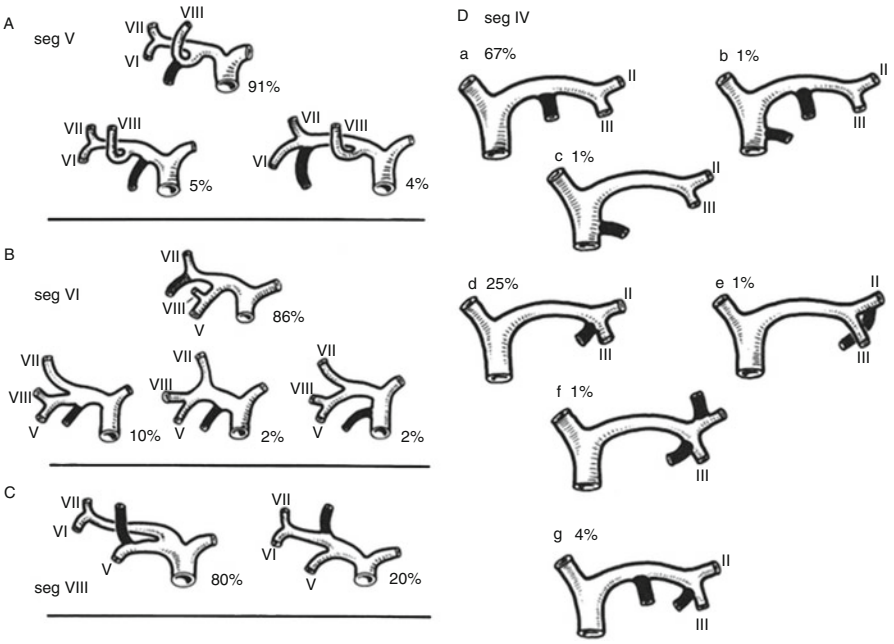

Fig. 1.5 Sketch shows the main variations of the intrahepatic ductal system. (**a**) Variations of segment V. (**b**). Variations of segment VI. (**c**) Variations of segment VIII. (**d**) Variations of segment IV. There is no variation of drainage of segments II, III, and VII. Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1B.26. p. 45

Extrahepatic Biliary Anatomy

The extrahepatic biliary system is represented by the extrahepatic segments of the left and right hepatic ducts, the biliary confluence, the common hepatic duct, the gallbladder and cystic duct, and the common bile duct.

Biliary Confluence

The right hepatic duct is characteristically short, measuring 0.9 cm, on average. In contrast, the left hepatic duct is typically 2.5 cm, though ranges from 2 to 5 cm [46]. Crossing anteriorly to their respective portal veins, the extrahepatic left and right ducts join at the hepatic ductal confluence anterior to the origin of the right branch of the portal vein within the liver hilum. Variations of the ductal confluence are common and are reported in nearly half of individuals (Fig. 1.6). Apart from the typical biliary confluence, the next most frequent configuration is a right anterior sectoral duct inserting directly into the common hepatic duct, as reported in 16 % of

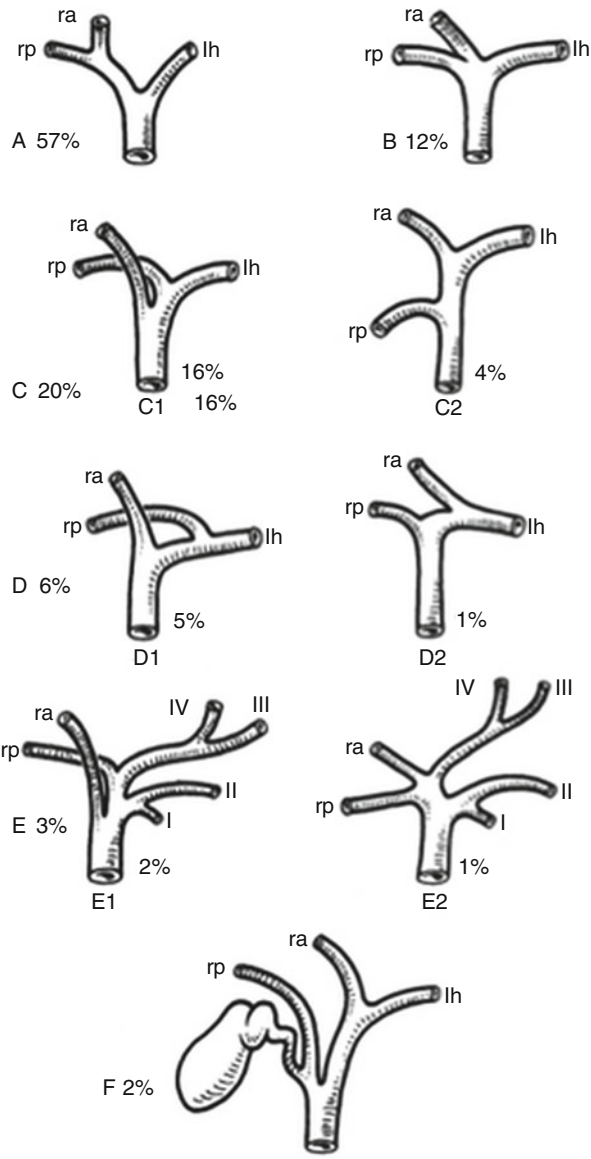

Fig. 1.6 Main variations of the hepatic duct confluence. (**a**) Typical anatomy of the confluence. (**b**) Triple confluence. (**c**) Ectopic drainage of a right sectoral duct into the common hepatic duct. (**d**) Ectopic drainage of a right sectoral duct into the left hepatic ductal system. (**e**) Absence of the hepatic duct confluence. (**f**) Absence of right hepatic duct and ectopic drainage of the right posterior duct into the cystic duct. *ra* right anterior, *rp* right posterior, *lh* left hepatic. Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1B.25. p. 44

cases. In 12 %, a trifurcation involving the right anterior, right posterior, and left hepatic ducts is seen [43, 44]. In these cases, the right posterior sectoral duct is three times more likely to be superior to the right anterior duct [44]. Ectopic drainage of the right posterior sectoral duct is seen in 11 % of individuals, with 5 % draining into the left hepatic duct, 4 % into the common hepatic duct, and 2 % into the cystic duct, a potentially dangerous anatomical variation should it not be properly identified during surgery of the gallbladder [43].

The ductal confluence and its corresponding vascular elements are enclosed in a sheath of connective tissue, known as the *hilar plate*, which is continuous with the hepatoduodenal ligament and fuses with Glisson's capsule on the posterior aspect of the quadrate lobe (segment IVb). By lifting up the quadrate lobe and incising the glissonian capsule at its junction with the hilar plate, good exposure of the hilar structures can be achieved, a technique known as *lowering of the hilar plate*. This is of particular importance when access to the left hepatic duct is required and, because the plane is largely devoid of vascular interpositions, it is relatively safe [42].

Common Bile Duct, Sphincter of Oddi, and Ampulla of Vater

The extrahepatic bile ducts contain columnar epithelium surrounded by a lamina propria rich in collagen and elastin fibers, and a layer of connective tissue. Muscle fibers are sparse and scattered, though a more developed muscle layer is seen distally as the bile duct enters the pancreas. The *common hepatic* duct begins at the biliary confluence and courses downward, anterior to the portal vein, at the free edge of the lesser omentum. After 2–3 cm, it is met by the cystic duct, at which point it becomes the *common bile* duct.

Approximately 8 cm in length with a normal diameter ranging from 4 to 9 mm, the common bile duct can be divided into three anatomic segments—supraduodenal, retroduodenal, and intrapancreatic. Like the common hepatic duct, the supraduodenal segment of the common bile duct runs at the free edge of the lesser omentum in the hepatoduodenal ligament, anterior to the portal vein and lateral to the hepatic artery. The retroduodenal segment passes posterior to the first portion of the duodenum and sits anterior to the inferior vena cava and lateral to the portal vein. The intrapancreatic portion lies on the posterior aspect of the pancreas within a tunnel or groove, where it is joined inferiorly by the pancreatic duct. Together they enter the second portion of the duodenum at an oblique angle, pass through the sphincter of Oddi, and finally terminate at the ampulla of Vater within the duodenal lumen [46].

The relationship between the common bile duct, the pancreatic duct, and their opening at the duodenal papilla is variable and occurs in three ways. Most often (60 %), the bile duct and the pancreatic duct together form a common duct, 1–8 mm in length. In 38 % of cases, however, a "double-barreled" opening is seen at the apex of the papilla. In these instances, the opening of the pancreatic duct is always inferior and anterior to that of the bile duct. Rarely (2 %), the two ducts have two separate openings in the duodenum [47, 48]. In the 5–10 % of individuals who have pancreas divisum (nonunion of the ventral and dorsal pancreatic buds), the ventral pancreatic duct joins the common bile duct and empties through the major papilla; the dorsal pancreatic duct empties through an accessory tract, the minor papilla [1]. In 75 % of individuals, the papilla is found on the posterior-medial aspect of the proximal to mid second portion of the duodenum. In 25 %, however, it is found lower, occasionally implanting in the third portion of the duodenum just right of the superior mesenteric artery [47].

The sphincter of Oddi is approximately 6 mm in length and is composed of thick bundles of circular, semicircular, and longitudinal muscle fibers, with numerous glands interspersed throughout. It exists separately from the surrounding muscle of the duodenum, from which it is distinguished by a plane known as the *duodenal window* [49]. Muscle fibers from the duodenum traverse the duodenal window and tether the sphincter of Oddi to the wall of the duodenum. Weak points in these fibers, particularly at the inferior aspect of the duodenal window, are susceptible to mucosal hernias. These diverticula may lead to sphincter of Oddi dysfunction and are suggested to play a role in some obstructive, inflammatory, and infectious processes of the pancreaticobiliary system [50, 51].

Gallbladder and Cystic Duct

The gallbladder is a pear-shaped reservoir that lies within the cystic fossa on the undersurface of the liver at the junction of segment V and IVb. An extension of the hilar plate, the *cystic plate* is a sheath of connective tissue fused with the underlying glissonian capsule that separates the gallbladder from the liver parenchyma. The gallbladder is typically 7–10 cm in length and 2.5–3.5 cm in width, although its size may vary considerably in fasting and post-prandial states, and in certain pathologic conditions. The gallbladder consists of a fundus, body, infundibulum, and neck, though these divisions are relatively arbitrary and imprecise. The tip of the fundus usually extends up to, or beyond, the free edge of the liver and is closely adherent to the cystic plate. The body of the gallbladder rests on the first and second portion of the duodenum and occupies the majority of the gallbladder fossa within the liver. The angled portion of the inferior body as it enters the neck is called the infundibulum, though this term is omitted in many classifications. When this portion is dilated, either as a normal anatomic variant or as sequela of chronic inflammation, the infundibulum produces an asymmetric bulge, known as a *Hartmann pouch* (Fig. 1.7b). It is important to note that the presence of this pouch may obscure the common hepatic duct, posing a real danger during cholecystectomy. If the pouch is large enough, the cystic duct may actually appear to enter the gallbladder mid-body, rather than at its apex, as is traditionally seen [52].

The cystic duct arises from the neck of the gallbladder and, coursing downward, joins the common hepatic duct at an acute angle to form the common bile duct. Its mucosa is arranged in spiral folds, referred to as the *valves of Heister*, although they have no known function. The length of the cystic duct depends on its point of union with the common hepatic duct, averaging 2–4 cm. Its luminal diameter usually measures 1–3 mm [42].

Many anomalies of the gallbladder and cystic duct have been described and vary in their incidence and clinical significance. In general, anomalies of the gallbladder can be divided into three groups based on formation, number, and position. Though of no pathological significance, a phrygian cap deformity is the most common anomaly of the gallbladder, seen in up to 18 % of individuals, and is formed by an

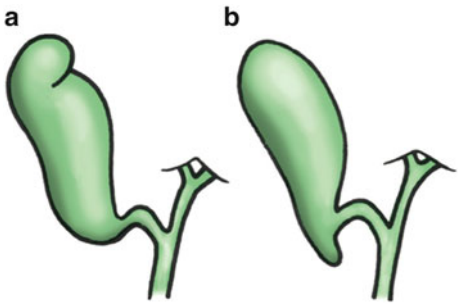

Fig. 1.7 (**a**) Phrygian cap deformity. (**b**) Hartmann pouch of the infundibulum. Gray SW, Skandalakis JE: Embryology for surgeons. Philadelphia: Saunders, 1972. p. 254

infolding or cleft at the base of the fundus [53] (Fig. 1.7a). Bilobar, hourglass, diverticular, and septated gallbladders have also been described [54–56] (Fig. 1.8b, c).

In approximately 1 in 4000 persons, a duplicated gallbladder may be seen (Fig. 1.8a). Existing and functioning as two separate cavities, each gallbladder may either have its own cystic duct that empties independently into the extrahepatic biliary tree, or they may merge into a common cystic duct before emptying into the common bile duct [57]. Although rare, agenesis of the gallbladder is also described, and may be seen in isolation or less frequently with other, often fatal, congenital anomalies. Despite an absent gallbladder, up to 50 % of these patients develop symptoms similar to biliary colic, though the cause is unclear [58].

Finally, anomalies of the position of the gallbladder can be seen, which most often include an intrahepatic, floating, or left-sided gallbladder. Intrahepatic gallbladders may be either partially or completely embedded within the liver parenchyma and should be suspected if ultrasound or cholecystogram reveals an unusually high gallbladder. Associated with gallstones in approximately 60 % of adults, these gallbladders may be challenging to remove during cholecystectomy. A floating gallbladder is a rare finding in which the gallbladder is completely surrounded by peritoneum and, rather than being tightly adherent, is freely suspended from the cystic fossa on the undersurface of the liver by a pedicle. This attachment may course the entire length of the gallbladder or involve only the cystic duct, leaving the gallbladder at risk for torsion and infarct [59]. Most commonly found on the undersurface of the left liver, left-sided gallbladders may be seen in isolation or in association with situs inversus [60].

Several anomalies of the cystic duct exist and primarily involve variations in length, course, and insertion into the common hepatic duct (Fig. 1.8d, e). An angular union between the cystic duct and common hepatic duct is most common, found in 75 % of individuals. In 15–20 %, the cystic duct may run parallel to the common hepatic duct for a variable distance before joining. In these cases, both ducts are encased in a sheath of connective tissue and care must be taken during dissection to avoid damage to either structure. In approximately 8 % of individuals, the cystic duct may spiral around the common hepatic duct, forming a left-sided union.

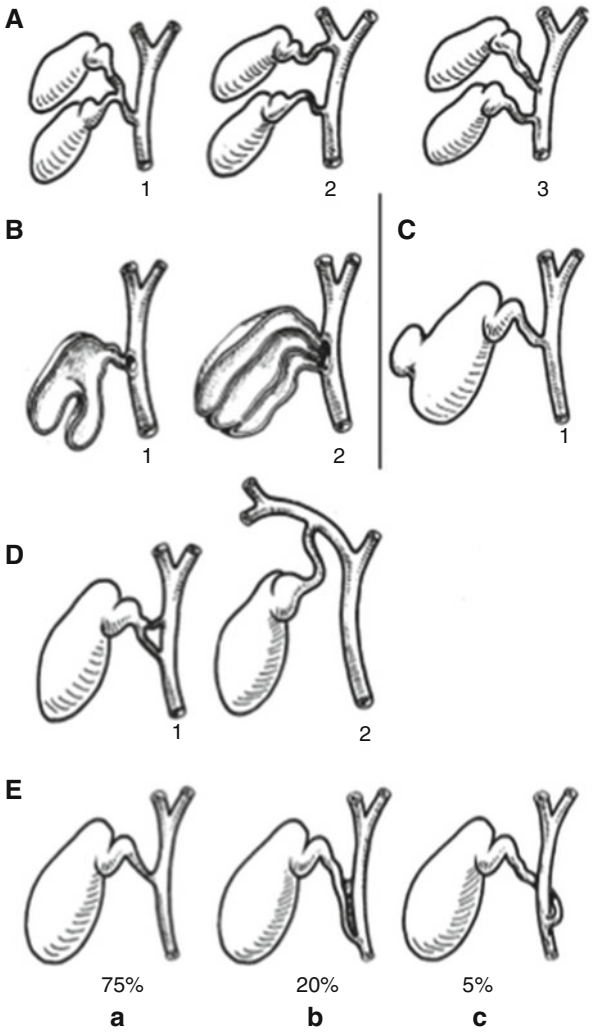

Fig. 1.8 Main variations in gallbladder and cystic duct anatomy: (**a**) Duplicated gallbladder. (**b**) Septum of the gallbladder. (**c**) Diverticulum of the gallbladder. (**d**) Variations in cystic ductal anatomy. (**e**) Different types of union of the cystic duct and common hepatic duct: angular union (*a*), parallel union (*b*), spiral union (*c*). Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1B.28. p. 46

Rarely, the cystic duct may insert into the right hepatic duct or form a trifurcation with the right and left hepatic ducts. In these situations, the right hepatic duct may easily be mistaken for the cystic duct and inadvertently ligated or divided, thus, underscoring the importance of adequate understanding and identification of these structures [61, 62].

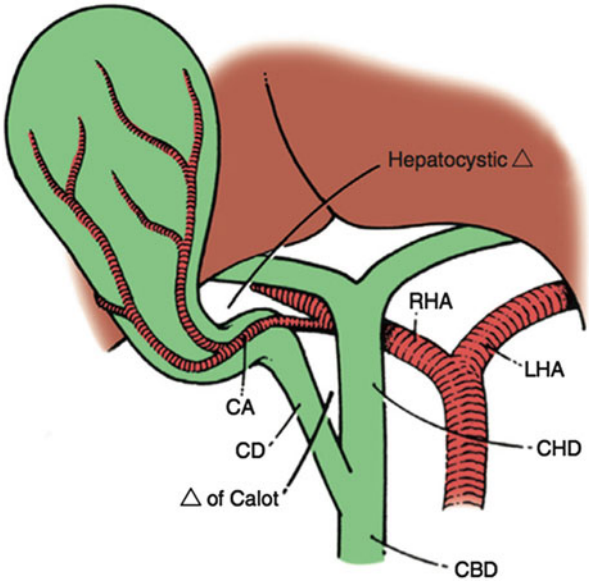

Fig. 1.9 The triangle (Δ) of Calot and the hepatocystic triangle. The upper boundary of the triangle of Calot is the cystic artery (CA), while that of the hepatocystic triangle is the inferior margin of the liver. *CBD* common bile duct, *CD* cystic duct, *CHD* common hepatic duct, *LHA* left hepatic artery, *RHA* right hepatic artery. Skandalakis JE, Gray SW, Rowe JS Jr: Biliary tract. In Skandalakis JE, Gray SW, editors: Anatomical complications in general surgery. New York, McGraw-Hill; 1983. p. 31

Triangle of Calot

The *triangle of Calot* was originally described in 1891 as a triangular anatomic region formed by the cystic artery superiorly, the cystic duct laterally, and the common hepatic duct medially. In the commonly accepted definition of this triangle, also known as the *hepatocystic triangle*, the inferior surface of the right lobe of the liver constitutes the upper border, rather than the cystic artery [63] (Fig. 1.9). Thorough anatomical knowledge of the triangle is of key significance, as several important structures pass through the area and must be identified when dissecting this region during cholecystectomy. The cystic artery is nearly always found within the triangle of Calot (96 %), and in 80 % of individuals its origin from either a normal or aberrant right hepatic artery is found within the triangle. The right hepatic artery passes posterior to the common hepatic duct in 85 % of individuals, as it ascends to the liver through the triangle of Calot; in 15 % it passes anterior to the common hepatic duct. When originating from the superior mesenteric artery (15 %), a replaced or accessory right hepatic artery may be found within the medial aspect of Calot's triangle. Aberrant hepatic ducts may also be found within the triangle, before joining the cystic or common hepatic duct [64].

Vasculature of the Biliary System

Bile Duct Blood Supply

The arterial blood supply to the right and left hepatic ducts, the biliary confluence, and the upper portion of the common hepatic duct comes from the surrounding left and right hepatic arteries and the cystic artery, forming a rich network on the surface of the ducts. The blood supply to the supraduodenal bile duct is mostly axial and is made up of an average of eight small arteries, with the majority arising from the superior pancreaticoduodenal artery, the right hepatic artery, the cystic artery, the gastroduodenal artery, and the retroduodenal artery. The most important of these ductal arteries run parallel along the lateral borders of the duct and are known as the *3 o'clock* and *9 o'clock arteries* (Fig. 1.10). Roughly 60 % of the blood supply to the supraduodenal bile duct originates inferiorly from the gastroduodenal, retroduodenal, and superior pancreaticoduodenal arteries. Conversely, 38 % of the blood supply originates superiorly from the right hepatic and cystic arteries. Only 2 % of the blood supply to the supraduodenal bile duct is nonaxial, arising directly from the proper hepatic artery as it courses within the hepatoduodenal ligament, parallel and

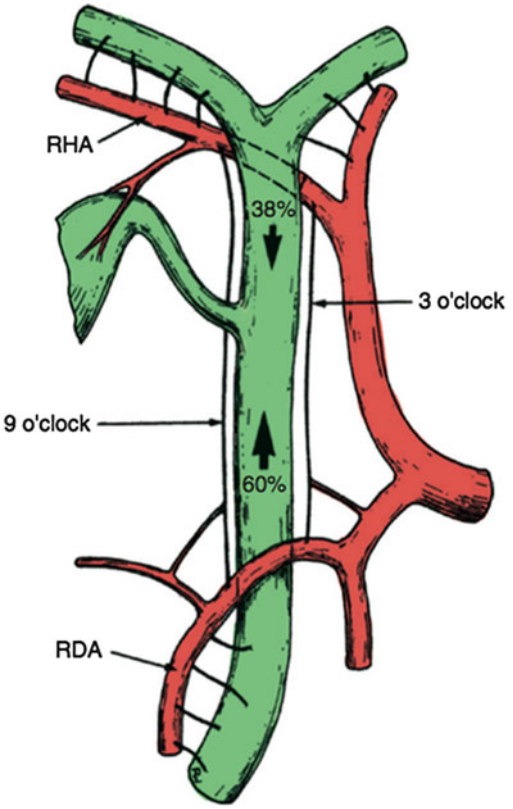

Fig. 1.10 Distribution of arterial blood supply to the extrahepatic biliary tree. *RDA* retroduodenal artery, *RHA* right hepatic artery. Terblanche J, Allison HF, Northover JMA. An ischemic basis for biliary strictures. Surgery. 1983; 94(1):56

to the left of the common bile duct. The retroduodenal and intrapancreatic portions of the common bile duct are supplied by the retroduodenal and pancreaticoduodenal arteries [65].

The venous drainage of the hilar hepatic ducts and the hepatic surface of the gallbladder occurs through small vessels that empty directly into branches of the surrounding hepatic veins within the liver. The veins draining the main bile duct run on either side of the duct as satellites of their corresponding arteries and drain into the liver separate from the portal vein, while venous drainage of the lower part of the bile duct runs directly into the portal vein [42].

Cystic Artery

The cystic artery usually arises as a solitary branch from the right hepatic artery within the triangle of Calot. The lymph node of Calot often lies just superficial to the cystic artery within the triangle and may serve as a guide to easily identify the artery. Running parallel and just medial to the cystic duct, the cystic artery supplies the duct with one or more small arterial branches. As it approaches the gallbladder, the cystic artery divides into a superficial branch, which runs along the anterior surface of the gallbladder, and a deep branch, which passes behind the gallbladder in the cystic fossa.

Occasionally, the cystic artery may arise from the common hepatic, left hepatic, gastroduodenal, or superior mesenteric arteries (Fig. 1.11). If the cystic artery arises from the proximal right hepatic artery or from the common hepatic artery, it often lies in close proximity to the hepatic duct, putting the latter at risk for injury during dissection [61, 66]. In the 20 % of patients whose cystic artery originates outside the triangle of Calot, the majority enter the triangle posterior to the common hepatic or common bile ducts. If the cystic artery crosses anterior to these ducts, it is often the first structure encountered during dissection, rather than the cystic duct, and usually requires early ligation and division to provide adequate exposure to the remaining structures [66]. In 15–20 % of individuals, a double or accessory cystic artery is seen. Rarely, a triple cystic artery may be seen [61, 67].

In approximately 10 % of individuals, the right hepatic artery runs across the triangle of Calot adjacent to the cystic duct before sharply turning upward toward the liver, giving it a tortuous or humped appearance. This is of particular importance in the 15 % of patients whose right hepatic artery runs anterior to the common hepatic duct. In these cases, the cystic artery often arises from the angled portion, also known as the *caterpillar hump*, of the right hepatic artery as it changes course. During cholecystectomy, this caterpillar hump may easily be mistaken for the cystic artery and inadvertently ligated. In addition, cystic arteries that arise from a caterpillar hump are often short and at risk for avulsion if excessive traction is applied to the gallbladder [61].

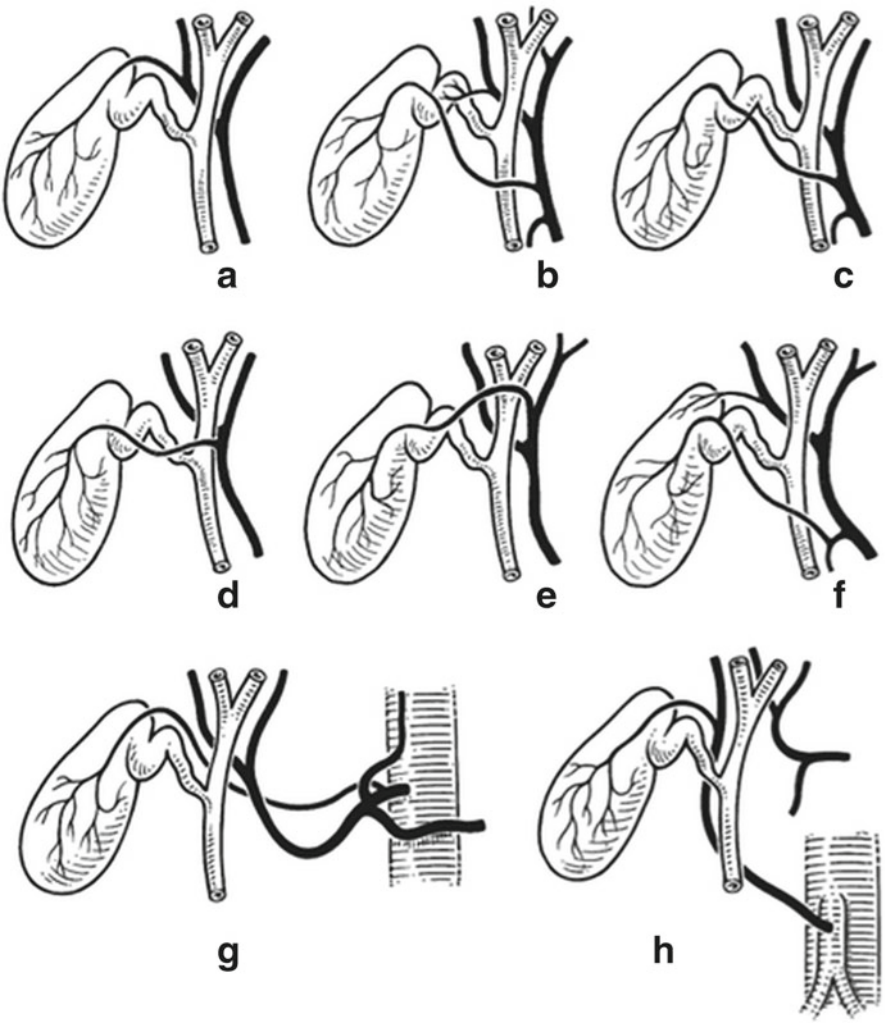

Fig. 1.11 The main variations of the cystic artery: (**a**) Typical course double. (**b**) Cystic artery. (**c**) Cystic artery crossing anterior to main bile duct. (**d**) Cystic artery originating from the right branch of the hepatic artery and crossing the common hepatic duct anteriorly. (**e**) Cystic artery originating from the left branch of the hepatic artery. (**f**) Cystic artery originating from the gastroduodenal artery. (**g**) Cystic artery arising from the celiac axis. (**h**) Cystic artery originating from a replaced right hepatic artery. Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 1B.22. p. 43

Lymphatic Drainage

The lymphatic drainage from the hepatic ducts and common bile duct is primarily to the hepatic lymph nodes within the hepatoduodenal ligament and along the hepatic artery. The lymphatics of the gallbladder partially drain into the liver, but also drain through the cystic duct node, located at the junction of the cystic duct and the common hepatic duct, before joining the hepatic lymph node chain. The lower portion of the bile duct drains via the superior pancreatic lymph nodes [42].

Neural Innervation

The nerve supply to the gallbladder and biliary tree comes from both sympathetic and parasympathetic nerve fibers derived from the celiac plexus that run along the hepatic artery [42].

Physiology

Overview

Bile secretion is one of the major functions of the liver and biliary tree and serves two major roles: the excretion of hepatic metabolites and organic solutes, and the facilitation of intestinal absorption of lipids and fat-soluble vitamins. Hepatocytes within the liver continuously synthesize and secrete bile, which collects in the intrahepatic canaliculi, flows out the liver through the bile ducts, and fills the gallbladder, where bile is concentrated and stored. When chyme reaches the small intestine, cholecystokinin (CCK) is secreted and stimulates contraction of the gallbladder and relaxation of the sphincter of Oddi. This allows stored bile to flow from the gallbladder into the lumen of the duodenum, where bile salts emulsify and solubilize dietary lipids. Once these lipids are absorbed, the bile salts are recirculated through the portal system to the liver via the enterohepatic circulation. Alterations in bile secretion and obstruction of flow due to various pathologic conditions and iatrogenic complications may contribute to the derailment of multiple organ systems and lead to significant patient morbidity and mortality [68].

Bile Composition

Bile is composed of several organic constituents secreted by hepatocytes, including bilirubin, bile salts, phospholipids, and cholesterol, in addition to electrolytes and water.

Bile Salts

Bile salts, which are steroid molecules synthesized by hepatocytes and include bile acids, constitute 50 % of the components of bile and are the major osmotic force behind bile flow. Formed at a rate of 500–600 mg per day, the total bile salt pool is approximately 2.5 g, with the bulk of the bile salts found in the gallbladder, followed by the liver, the small intestine, and the extrahepatic bile ducts.

Four bile acids are present in humans: two primary and two secondary bile acids. The two primary bile acids are synthesized from cholesterol by hepatocytes via two main pathways. The *classic pathway*, the primary mode of bile acid synthesis, leads to the formation of cholic acid, which constitutes the vast majority of the bile acid pool. The *alternate pathway* leads to the formation of chenodeoxycholic acid. Once secreted into the lumen of the intestine, a small percentage of the cholic and chenodeoxycholic acids are dehydroxylated by intestinal bacteria, producing the two secondary bile acids: deoxycholic acid and lithocholic acid, respectively [68, 69].

The liver conjugates the four bile acids with one of two amino acids, glycine or taurine, to form a total of eight bile salts, each named for the composing bile and amino acids. This conjugation is a critical step in bile function, as it changes the bile acids, which are insoluble in the acidic environment of the duodenum, into the much more water-soluble bile salts. Bile salts are amphipathic, meaning they have both hydrophilic and hydrophobic portions, a property critical to solubilize lipids. The first role of bile salts is to emulsify lipids in order to maximize surface area for digestion. This occurs when the negatively charged bile salts surround the lipids, creating small lipid droplets dispersed within the intestinal lumen. Next, bile salts form micelles, which contain a core of lipid breakdown products, including monoglycerides, lysolecithin, and fatty acids, and a surface lined with bile salts. The hydrophobic portion of the bile salts dissolves in the lipid core, while the outward pointing hydrophilic portion dissolves in the aqueous duodenal environment.

Phospholipids and Cholesterol

Phospholipids and cholesterol are primarily synthesized in the liver from low-density lipoproteins circulating in plasma and from de novo pathways, with only a small percentage of cholesterol coming from dietary sources. The primary phospholipid in human bile is lecithin, representing 95 % of its total. Though their role in bile secretion is largely secondary compared to bile salts, biliary lipids play an important role in cholesterol excretion, intestinal absorption of lipids, and protection of biliary epithelial cells against bile acid-induced injury [70].

Phospholipids and cholesterol are secreted into bile by hepatocytes and are included in micelle formation, with hydrophobic cholesterol joining the lipid degradation products within the core and the amphipathic phospholipids providing structural support. This bile salt-phospholipid-cholesterol complex, however, is not the only carrier of biliary cholesterol. Unilamellar vesicles made up of a phospholipid

and cholesterol bilayer can be seen in various concentrations in human bile (Fig. 1.12). In states of excess cholesterol, these vesicles can aggregate, forming large, multilamellar vesicles. When the bile concentration of cholesterol becomes supersaturated and exceeds the transport capacity of these vesicles, liquid crystals of cholesterol monohydrate can form, known as *cholesterol nucleation*, a precursor condition in cholesterol gallstone formation [71].

Bilirubin

Bilirubin serves as the major bile pigment, giving it its characteristic yellow color. A by-product of senescent erythrocyte degradation by the reticuloendothelial system, heme is the source of 80–85 % of the daily bilirubin production, with the remaining percentage derived from breakdown products of hepatic hemoproteins. Found in high concentrations in the liver, spleen, and bone marrow, the enzyme heme oxygenase plays a major role in the initial conversion of heme to biliverdin, though both enzymatic and nonenzymatic pathways have been proposed. Biliverdin is then reduced to bilirubin in a nicotinamide adenine dinucleotide (NADH)-dependent reaction by biliverdin reductase prior to being released into the circulation. In this form, bilirubin is "unconjugated" and poorly soluble, requiring that it be bound to plasma proteins, primarily albumin, as it is transported through the circulation for further processing by the liver.

Once extracted from the blood, bilirubin binds to a driver of glutathione-S-transferase within the hepatocyte and is catalyzed by bilirubin uridine-5-diphosphate (UDP)-glycosyltransferase to form bilirubin glucuronide, the water-soluble, "conjugated" form of bilirubin. Mutations in the bilirubin UDP-glycosyltransferase gene have been implicated in the Crigler-Najjar and Gilbert syndromes, both characterized by unconjugated hyperbilirubinemia [72]. Conjugated bilirubin is secreted as a component of bile into the intestine, where it is converted back to unconjugated bilirubin, then to urobilinogen by intestinal bacteria. A portion of the urobilinogen produced is then recirculated to the liver, a portion excreted in the urine, and the remainder is oxidized to urobilin and stercobilin within the intestine, giving stool its characteristic dark brown color [68].

Water and Electrolytes

The final components of bile are electrolytes and water, which are secreted by the epithelial cells lining the bile ducts in response to stimulation by numerous gastrointestinal hormones. Water constitutes 85 % of the volume of bile leaving the liver.

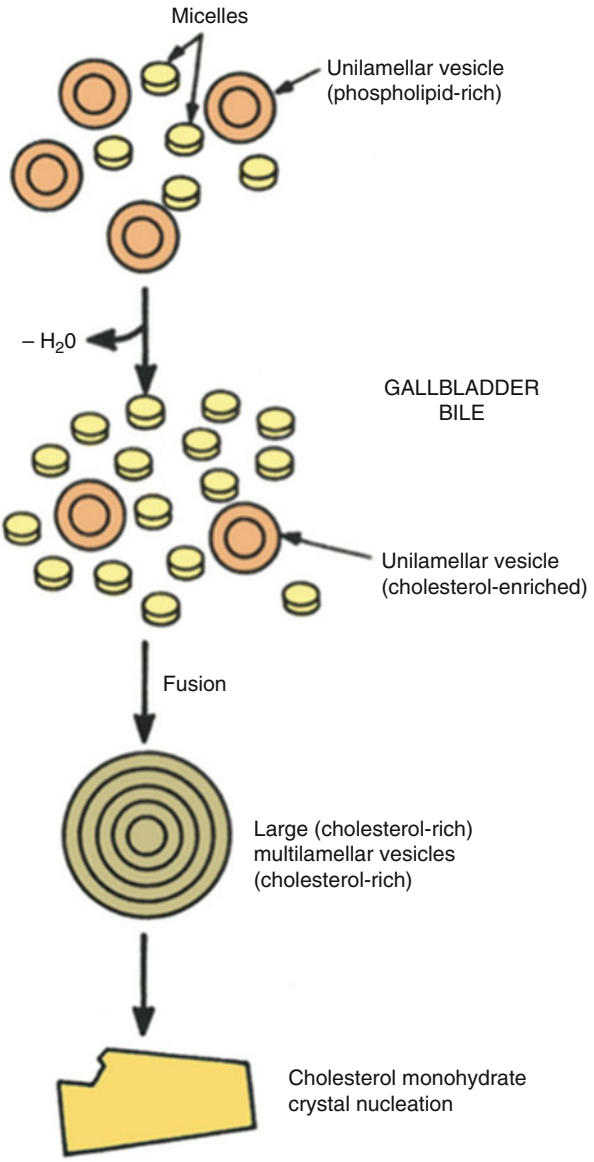

Fig. 1.12 Concentration of bile leads to net transfer of phospholipids and cholesterol from vesicles to micelles. Phospholipids are transferred more efficiently than cholesterol, leading to cholesterol enrichment of the remaining (remodeled) vesicles. Aggregation of these cholesterol-rich vesicles forms multilamellar liquid crystals of cholesterol monohydrate. Pitt HA, Nakeeb A, Espat NJ. Bile secretion and pathophysiology of biliary tract obstruction. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. Vol. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 7.2. p. 115

Bile Secretion

Hepatocytes are arranged in plates along vascular network connecting the portal to the central venous system. The small apical domains of adjacent hepatocytes within these plates form tubular lumen, known as canaliculi. Normally in a low-pressure system (5–10 cm H_2O), bile is secreted into the canalicular network by the active transport of solutes followed by the passive flow of water. Roughly 750–1000 mL of bile is secreted by the liver daily, which depends on neurogenic, humoral, and chemical control. Bile secretion is increased by vagal stimulation, while hepatic vasoconstriction, seen during splanchnic stimulation, results in decreased bile secretion. Various gastrointestinal hormones, including secretin, CCK, and gastrin, play a role in increasing bile flow. The most important factor in the regulation of bile flow, however, is the rate of hepatocyte bile salt synthesis, which is largely dictated by the recycling of bile salts via the enterohepatic circulation.

Bile Salt Secretion

In plasma, bile acids are bound to either albumin or lipoproteins. Their uptake from the space of Disse within the liver into hepatocytes is mediated by sodium-dependent and sodium-independent mechanisms. Several transport proteins have been identified as playing key roles in this process. The *sodium-taurocholate cotransporting polypeptide* (NTCP) is a bile salt transporter found exclusively on the basolateral membrane of hepatocytes and is responsible for 80 % of taurocholate uptake. In contrast, the *organic anion transporting polypeptides* (OATPs) are a family of sodium-independent transporters that mediate the uptake of a broad variety of organic anions, of which bile acids are only one of their many substrates [73, 74].

Two primary mechanisms have been suggested to control bile acid intracellular transport: one involves the transport of bile acids from the basolateral to the canalicular membrane through bile acid-binding proteins, while the other depends on the vesicular transport of bile acids [75]. Regardless of the method of intracellular transport, the transport of bile salts across the hepatocyte canalicular membrane represents the rate-limiting step in the overall secretion of bile salts.

The concentration of bile salts within the canaliculi is 1000 times greater than in the hepatocytes, necessitating an ATP-dependent, active transport of solutes. This is largely mediated by the bile salt export pump (BSEP), which is closely related to the proteins of the multidrug resistant (MDR) gene family of ATP binding cassette (ABC) transporters, and serves as the major transporter of monovalent bile salts into the canaliculi [73]. MDR-related protein-2 (MRP2) has also been shown to transport certain bile salts into the canaliculi, along with the export of other organic solutes, including conjugated bilirubin, chemotherapeutic agents, antibiotics, toxins, and heavy metals [76, 77].

Biliary Lipid and Cholesterol Secretion

The secretion of phospholipids involves the translocation of phosphatidylcholine from the inner to the outer leaflet of the canalicular plasma membrane, which is mediated by the MDR3 transporter. Defects in MDR3 expression are thought to cause progressive familial intrahepatic cholestasis type 3, a rare autosomal recessive disorder marked by progressive liver disease. Because these patients lack phosphatidylcholine in their bile, which normally protects biliary epithelium from the toxic injury of bile salts, early childhood cholestasis, cholestasis of pregnancy, and progressive liver failure can occur [78]. In addition, some genetic variations of *MDR3* have been associated with increased susceptibility to drug-induced liver injury and primary biliary cirrhosis [79, 80].

Less is known about cholesterol secretion, although several studies have shown that the ABC transporters, ABCG5 and ABCG8, may play an important role. Mutations in these transporters are seen in patients with sitosterolemia, a rare autosomal recessive disorder characterized by intestinal hyperabsorption of all sterols, including cholesterol, coupled with the impaired ability to excrete these sterols in bile [81]. In more recent years, the cholesterol-lowering drug, ezetimibe, has been suggested to target ABCG5 and ABCG8 by indirectly upregulating their expression in the liver [82].

Bilirubin Secretion

The liver is the only organ in the body capable of removing the bilirubin-albumin complex from the circulation. On the basolateral membrane of hepatocytes, both conjugated and unconjugated bilirubin are taken up by the membrane transporters OATP1B1 and OATP1B3, both members of the OATP transporter family mentioned previously [83]. Because of its lipid soluble properties, unconjugated bilirubin can additionally cross the sinusoidal membrane by passive diffusion. Once conjugated, bilirubin glucuronides are excreted into the biliary canaliculi via the ATP-dependent MRP2 transporter. As previously mentioned, MRP2 has a broad substrate affinity and is responsible for the transport of a wide spectrum of organic ions [76, 77]. Interestingly, a substantial percentage of conjugated bilirubin is returned to the sinusoidal membrane and secreted back into plasma by MRP3, where it is taken up by downstream hepatocytes via their OATP1B1/3 transporters. This observed phenomenon is thought to prevent the saturation of the biliary secretory capacity of the hepatocytes surrounding the portal tracts by shifting some of the substrate burden toward those hepatocytes downstream near the central vein [84].

Bile Flow

Although bile salt secretion by hepatocytes is the principle driver of bile flow, it is regulated in part by other external factors. As bile passes through the biliary ductal network, its concentration is altered by the absorption and secretion of water and

electrolytes by cholangiocytes. Transcellular movement of water across cholangiocyte membranes is mediated by the uniquely co-expressed aquaporin channels, AQP1 and AQP4 [85]. Bicarbonate secreted by the Cl^-/HCO_3^- exchanger (AE2) and chloride secreted by cystic fibrosis transmembrane conductance regulator (CFTR) are also thought to play an important role in ductal bile flow, independent of bile salt secretion. In addition, the gastrointestinal hormone secretin has been shown to stimulate the exocytic insertion of vesicles containing AQP1, AE2, and CFTR, thus demonstrating its role in increasing ductal bile flow [86].

Gallbladder Function

The gallbladder's primary function is to store bile, concentrate bile, and when stimulated to contract in response to a meal, in a coordinated manner, eject bile. To accomplish this, the gallbladder has unique absorptive, secretory, and motility capabilities.

Absorption

The normal storage capacity of the human gallbladder is 40–50 mL. This seemingly minute fraction of the total bile produced by the liver per day is overcome by the gallbladder's remarkable absorptive ability, concentrating bile as high as tenfold. Indeed, the gallbladder epithelium has one of the highest rates and capacities to absorb water and electrolytes in the body [87]. The transport of water by gallbladder epithelia occurs through AQP1 and AQP8, and is a passive process secondary to the active transport of solutes, namely via Na^+/H^+ and Cl^-/HCO_3^- exchangers [88]. In this way, water is absorbed in an isosmotic fashion, meaning that an osmotic equilibrium is maintained across the absorbed and luminal solutions. However, because the net transport of water is always coupled in the same direction with sodium and chloride transport, water absorption in the gallbladder occurs against its chemical gradient (i.e., from the concentrated lumen into the dilute intracellular environment of the gallbladder epithelia) [89, 90].

As the gallbladder mucosa readily absorbs water, the concentration of biliary lipids, bile salts, bilirubin, and cholesterol increases, making the environment ripe for solute precipitation and gallstone formation. Although some calcium (Ca^{2+}) is absorbed by the gallbladder epithelium, its absorption is not as efficient as that of water, leading to a relative increase in luminal Ca^{2+} concentration. Elevations in gallbladder Ca^{2+} coupled with increased concentrations of unconjugated bilirubin, as may be seen in patients with hemolysis, alcoholism, ileal disease, and TPN dependence, lead to the precipitation of calcium bilirubinate crystals and pigmented gallstones [91].

The increased concentration of bile within the gallbladder also has effects on the solubility of cholesterol. Although the solubility within micelles increases, the stability of phospholipid-cholesterol vesicles decreases with increasing cholesterol

concentrations, and as a result, there is an increased tendency to form aggregate vesicles and cholesterol crystals [69]. Furthermore, increased concentrations of luminal Ca^{2+} ions have been shown to disrupt the structural integrity of the phospholipid-cholesterol vesicles, facilitating cholesterol nucleation and stone formation [92]. In addition, it has also been suggested that the presence of calcium bilirubinate crystals may further promote cholesterol precipitation by serving as a nidus to which it adheres [93].

Secretion

Though initially thought to only have absorptive capabilities, the gallbladder mucosa is responsible for the secretion of two important products: mucin and hydrogen ions (H^+). Synthesized and secreted by the surface mucous and submucosal glandular cells primarily lining the gallbladder neck and cystic duct, mucin serves as a lubricant and an important protective barrier against the detergent effect of highly concentrated bile acids on the gallbladder mucosa. However, numerous animal and human studies have demonstrated the pronucleating effects of mucin in gallstone disease [94–96]. Furthermore, bile from patients with gallstones has been shown to contain higher concentrations of mucin than from controls. Though the exact mechanism by which mucin promotes gallstone formation is unknown, it is thought that the plentiful hydrophobic binding sites within mucin's polypeptide core create a favorable environment for phospholipid-cholesterol vesicle aggregation and cholesterol nucleation [97]. Prostaglandins, the caustic effects of bile salts, and local inflammation have all been shown to stimulate gallbladder mucin secretion and are thought to play a role in mucin hypersecretion and gallstone formation [98, 99].

The intraluminal transport of hydrogen ions via the Na^+/H^+ exchanger coupled with the reabsorption of HCO_3^- via luminal membrane carbonic anhydrases leads to a decrease in bile pH from 7.5 to 7.8 down to 7.1 to 7.3 [100, 101]. This acidification of bile within the gallbladder promotes calcium solubility and thus is crucial in preventing calcium precipitation and gallstone formation.

Motility

Gallbladder filling and emptying is a dynamic process in response to a complex web of neural, hormonal, and mechanical interactions. Motor activity of the gallbladder occurs in response to, as well as in the absence of, food. During fasting states, known as the *interdigestive phase,* gallbladder motility is characterized by periods of filling, facilitated by gallbladder wall relaxation coupled with the tonic contraction of the sphincter of Oddi, followed by periods of partial emptying, controlled largely by the hormone motilin. Coordinated with the cyclic contractile activity of phase III of the intestinal migrating motor complex (MMC), these brief spurts of gallbladder contraction result in the emptying of 20–30 % of its volume every 1–2 h and are thought to play an important "housekeeping" role [102, 103]. First, the

delivery of small amounts of bile into the duodenum is thought to assist the MMC in cleansing the small intestine of residual food after digestion. It has also been suggested that partial gallbladder emptying and refilling results in the vigorous mixing of concentrated gallbladder bile with fresh, dilute hepatic bile, thereby preventing supersaturation and accumulation of cholesterol crystals and debris. In the instance that cholesterol crystals do form, these periodic contractions may allow for their ejection, thus preventing their further compaction and stone formation [102]. In several animal studies, vasoactive intestinal peptide (VIP) and nitric oxide (NO) have also been hypothesized to play a role in gallbladder motility during the filling portion of the interdigestive phase, primarily through smooth muscle relaxation of the gallbladder wall [102].

Following a meal, the gallbladder contracts in response to the potent stimulating effects of CCK, emptying 70–80 % of its contents over 30–40 min. CCK is also responsible for the coordinated relaxation of the sphincter of Oddi during this period. Receiving both sympathetic and parasympathetic nerve fibers, gallbladder motility is also under neural influence. During post-prandial and fasting states, gallbladder contractility is controlled by cholinergic vagal pathways via muscarinic receptors [104].

Impaired gallbladder motility is thought to play an important role in gallstone formation, as prolonged residence of bile within the gallbladder increases the opportunity for cholesterol nucleation and crystal formation. In addition, the loss of periodic gallbladder emptying results in fewer crystals being released into the duodenum [105]. Various conditions and medications have been implicated in gallbladder dysmotility. Patients with celiac disease, growth hormone deficiency, irritable bowel syndrome, chronic pancreatitis, hypertriglyceridemia, and somatostatinoma are thought to have decreased gallbladder motility through the inhibited release of or impaired response to endogenous CCK. This has also been demonstrated in patients receiving chronic TPN and octreotide therapy. In patients with autonomic neuropathy, as seen in diabetes and β-thalassemia, and in those who have had total or partial gastric resections, the disruption in vagal stimulation is thought to cause impaired gallbladder motility [106]. Medications affecting smooth muscle tone, such as calcium channel blockers, progesterone, loperamide, and spasmolytics, have all been suggested to decrease gallbladder contractility [107].

Just as gallbladder motor function can influence bile composition, so too can the components in bile affect gallbladder motility. Cholesterol hypersaturation is thought to induce excess accumulation of bile within the cell walls of gallbladder smooth muscle, resulting in decreased membrane fluidity and both impaired smooth muscle contractility and relaxation [106]. Increased mucin production may accelerate this process by increasing cholesterol absorption by the gallbladder wall [108]. Interestingly, the proliferative effects of cholesterol on arterial myocytes during atherogenesis are similar to those seen on gallbladder smooth muscle, suggesting a form of gallbladder hypertrophic leiomyopathy [109]. In animal models, bile acids, particularly the more hydrophobic ones, have been shown to cause muscle cell dysfunction through the production of free radicals, suggesting their potential role in gallbladder dysmotility in humans [110].

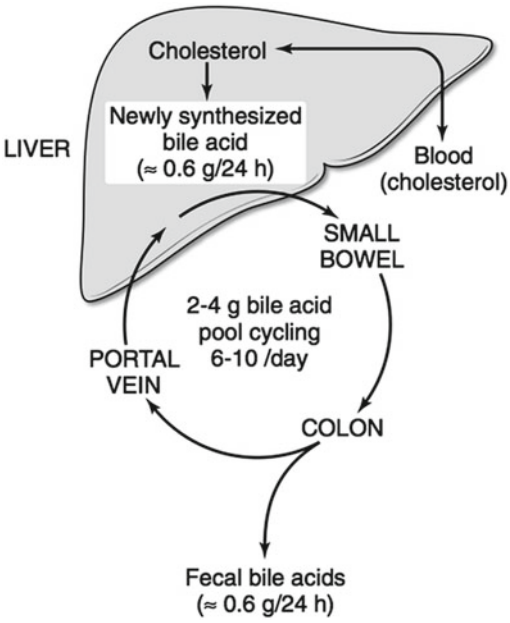

Fig. 1.13 Enterohepatic circulation of bile salts. Cholesterol is taken up from plasma by the liver. Bile acids are synthesized at a rate of 0.6 g/24 h and are excreted through the biliary system into the small bowel. Most of the bile salts are reabsorbed in the terminal ileum and are returned to the liver to be extracted and reextracted. Pitt HA, Nakeeb A, Espat NJ. Bile secretion and pathophysiology of biliary tract obstruction. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. Vol. 1. 5th ed. Philadelphia: Elsevier; 2012. Figure 7.3 p. 116

Enterohepatic Circulation

Bile salts are synthesized and conjugated in the liver, secreted in bile, stored in the gallbladder, ejected into the duodenum, reabsorbed by the small intestine (primarily the ileum), and returned to the liver via the portal venous system. This liver-intestinal cycling of bile, known as the *enterohepatic circulation*, completes 6–10 times daily and is responsible for the intestinal reabsorption of nearly 95 % of bile acids. The total amount of bile salt involved in the enterohepatic circulation is called the *circulating bile pool*, which equals roughly 2–4 g in normal human adults (Fig. 1.13). Nearly 90 % of the bile salt pool is sequestered in the gallbladder during periods of fasting.

In cases where there is an excess loss of bile salt, such as in ileal Crohn's disease, through biliary fistula, or with bile-binding products, an increase in bile salt production is seen. In this way, the enterohepatic circulation serves an important negative feedback role, maintaining a constant bile salt pool size [69].

Biliary Obstruction and the Pathophysiology of Jaundice

Obstruction of the biliary tract is a common and often challenging problem faced by general and hepatobiliary-trained surgeons. The causes of biliary obstruction are many and may be broken down into four categories: those conditions causing complete obstruction, such as common bile duct ligation or injury; intermittent

Table 1.1 Conditions commonly associated with biliary tract obstruction

Complete obstruction
Pancreatic head tumors
Common bile duct ligation or transection
Cholangiocarcinoma
Parenchymal liver tumors
Intermittent obstruction
Choledocholithiasis
Periampullary tumors
Duodenal diverticula
Choledochal cysts
Polycystic liver disease
Biliary parasites
Hemobilia
Chronic incomplete obstruction
Common bile duct strictures
Congenital
Traumatic/Iatrogenic
Primary sclerosing cholangitis
Post radiation therapy
Stenosis of biliary-enteric anastomosis
Chronic pancreatitis
Cystic fibrosis
Sphincter of Oddi stenosis
Segmental obstruction
Traumatic/Iatrogenic
Intrahepatic stones
Cholangiocarcinoma

Blumgart LH, Hann LE. Surgical and radiologic anatomy of the liver, biliary tract, and pancreas. In: Jarnagin WR, editor. Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas. 1. 5th ed. Philadelphia: Elsevier; 2012. Table 7.3 p. 117

obstruction, such as choledocholithiasis and choledochal cysts; chronic incomplete obstruction, such as biliary strictures, sclerosing cholangitis, and chronic pancreatitis; and segmental obstruction, such as an isolated sectoral duct injury (Table 1.1). Regardless of etiology, all patients with biliary obstruction are at risk for developing hyperbilirubinemia, whose manifestations may range from symptomatic (fevers, pain, pruritis) to clinical jaundice. If prolonged, fibrosis of the liver and biliary tract, cirrhosis, and eventual liver failure may develop. In addition to derangements in liver and biliary function, jaundiced patients are at increased risk of cardiovascular compromise, renal failure, coagulopathies, malnutrition, inadequate wound healing, and immune dysfunction, and carry a higher risk of perioperative mortality (Table 1.2) [101].

Table 1.2 Potential multisystem effects of biliary obstruction and jaundice

Hepatobiliary
Dilated bile canaliculi, distortion and swelling of microvilli
Hepatic ductule proliferation (chronic obstruction)
Inflammatory infiltration and fibrosis
Mucosal atrophy and squamous metaplasia of extrahepatic bile ducts
Impaired micro- and macrovascular perfusion to liver
Decreased bile secretion
Impaired excretion of drugs and toxins (antibiotics, endotoxin)
Decreased liver metabolism (inhibition of cytochrome P450 enzymes)
Hepatocyte apoptosis
Decreased hepatocyte synthetic function (albumin, clotting factors, IgA)
Impaired Kupffer cell function
Increased systemic proinflammatory cytokines (TNF-α, IL-6)
Cardiovascular
Decreased cardiac output
Impaired cardiac contractility
Blunted response to β-agonist drugs
Decreased peripheral vascular resistance
Renal
Decreased renal perfusion
Inappropriate diuresis
Endotoxin-mediated tubular and cortical necrosis
Coagulation
Decreased production of vitamin K-dependent clotting factors
Endotoxin-mediated platelet dysfunction
Immune
Impaired delayed-type hypersensitivity
Impaired T-cell proliferation
Decreased neutrophil chemotaxis
Defective phagocytosis
Bacterial intestinal translocation
Wound healing
Decreased collagen synthesis

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Summary

Over the last century, studies of the biliary tract—how it's formed, how it's arranged, and what functions it serves—on micro- and macroscopic levels have improved our understanding of normal biliary embryology, anatomy, and physiology tremendously. Perhaps more importantly, though, it has broadened our appreciation for the abnormal and given us a foundation from which we may begin to anticipate, mitigate, and manage biliary pathology and injury.

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