Diseases of the Liver and Biliary System in Children
Dedication
To my grandchildren, Finlay and Nina Parker, and all the children whom I have had the privilege to care for.
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Although the Ancient Egyptians believed that the liver had mystic powers of healing, and Hippocrates gave a full description of hepatic encephalopathy, modern hepatology has only taken off in the last 50 years. Accelerated progress has followed discovery of the hepatitis viruses, now a virtual alphabet from A to E and beyond. Hepatobiliary imaging and endoscopy have added to the progress. Developments have depended not only on specialist hepatologists, but on developments in other related disciplines of medicine – particularly virology, immunology, biochemistry, and now, molecular medicine. A huge literature is available describing liver disease in adults, but pediatrics has lagged behind.

This book covers all the essentials of pediatric hepatology and is therefore particularly timely. The material covered is wide, from such aspects as the psychology of parents of children on transplant waiting lists to the genetic disturbances of bilirubin and bile salt transport in the neonate. The chapter authors have been well chosen. They are international authorities, active both clinically and in research. They write lucidly from personal experience.

Many helpful algorithms and tables are included. The references at the end of each chapter have been carefully selected and are up-to-date… This book should be available in every pediatric department. It should be at hand at all times to offer practical advice on any childhood liver disease. General pediatricians will certainly benefit. It would be a suitable gift to reward a trainee.

This book fills a real gap in our knowledge of liver disease. It will be a well-deserved success.

Professor Dame Sheila Sherlock
1918–2001

Foreword to the First Edition
The diagnosis and management of pediatric liver disease has been transformed since the first edition of this book in 1999.

The rapid developments in cellular and molecular genetic techniques have identified new genes, discovered the causes of rare diseases, taught us much about pathophysiology, and revealed new targets for therapy.

National and international networks utilizing clinical biobanks and databases have helped us consolidate our knowledge and treatment of cholestatic liver disease, biliary atresia, and acute liver failure.

The medical management of pediatric liver disease owes much to the development of new drugs, particularly antiviral therapy, which has changed the outcome for many children and significantly improved the quality of their lives.

The successful development of transplantation, now extended to multiorgan transplantation, has dramatically improved the outcome of infants and children with liver or metabolic disease so that many have become adults, completed their education, and contribute equally to society. This means that it is important for adult hepatologists not only to become familiar with pediatric diseases new to them, but also to learn how best to manage young people with a lifetime of chronic illness.

The investigation and management of most pediatric liver disease should be based in specialist or transplant units so that patients benefit from centralized expertise. Nevertheless, it is essential for general pediatricians to recognize the early presentation of liver disease, know when to refer to a specialized unit, and be aware of the range of new therapies and their complications, especially transplantation.

The fourth edition of this book summarizes the advances of the last few years, and provides a practical approach to the diagnosis and management of pediatric liver diseases, highlighting the importance of multidisciplinary team working and holistic management of the child and family.

The remit has been extended to include information on structure and function, immunology, and genetics with an emphasis on basic mechanisms of disease. New chapters describe the effects of liver and kidney disease, combined liver and kidney transplantation, the management of anesthesia and intensive care for children with liver disease, and a summary of what the adult hepatologist needs to know.

The book should interest the adult gastroenterologist and hepatologist, the general pediatrician, and pediatric trainee as well as provide guidance to nurses and allied health professionals.

Deirdre A. Kelly
The investigation and management of pediatric liver disease requires skill, compassion and a dedicated multidisciplinary approach. I am indebted to my colleagues in the Liver Unit, in Birmingham Children's Hospital NHS Foundation Trust and elsewhere in the world for their expert knowledge and help with this book, which we hope will aid the management of children with liver disease everywhere.

I am particularly grateful to Angela Green for her help in coordinating the work for this book.

Deirdre A. Kelly
SECTION 1

Understanding the Liver
CHAPTER 1
Structure, Function, and Repair of the Liver

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Key points

• The subdivision of the liver into segments by the Couinaud system, with an independent arterial, portal venous, and biliary supply has important implications for liver (transplant) surgery.
• Blood flows in the portal vein and hepatic artery are closely linked, with obstruction of one vessel leading to compensatory flow rates in the other (hepatic arterial buffer response).
• 50% of hepatic oxygen supply is provided by the portal vein so the liver can maintain function for weeks without arterial blood supply. Bile duct epithelial necrosis is the first sign of an inadequate oxygen supply.
• Hepatocytes are polar cells with a basal domain contacting the fenestrated sinusoids for blood supply and an apical domain where bile is drained into the bile canaliculus.
• Proliferation and development of the intrahepatic biliary system continue until around 15 years of age, which must be taken into account when interpreting liver histology in children.
• Several hepatic enzymes are not fully expressed in newborn children, with immaturity of UDP-glucuronyl-transferase being an important factor in physiological jaundice of the newborn.
• Alpha-fetoprotein levels may exceed levels of 100,000 ng/mL in the healthy newborn, only reaching normal levels at 1 year of age, and is not necessarily a sign of malignancy.
• After trauma or partial hepatectomy, the liver regenerates by proliferation of mature hepatocytes within weeks.

The liver has fascinated mankind ever since medicine existed. Our knowledge, however, about the anatomy, structure, and function of the liver has changed dramatically over the last 1800 years. Ancient medicine was aware of the liver’s central role in nutrition, and for Galen it was a “principal instrument” of the body. In Greek mythology, Prometheus – the friend of mankind who was chained to a rock by the god Zeus as punishment for giving humans the use of fire – suffered daily as an eagle devoured his liver, only for it to restore itself overnight. This association with Prometheus and the capacity of the liver to regenerate has been quoted many times in textbooks, editorials, and reviews.

Patients and families find it difficult to understand the role of the liver and the implications of liver failure, and this has to be taken into consideration when counseling children and their families. In order to gain an understanding of liver disease, it is necessary to study the basics of the development, anatomy, and function of the liver and its responses to injury.

Structure
Development
Overview
Embryonal organ development derives from the three germ layers: endoderm, mesoderm, and ectoderm. Human liver development begins during the third week of gestation from the ventral foregut endoderm cells (the future duodenum), by differentiation into hepatoblasts triggered by cytokine fibroblast growth factor (FGF) and bone morphogenetic protein (BMP). The hepatoblasts are precursor cells of hepatocytes and cholangiocytes, they express organ-specific proteins α-fetoprotein (AFP) and albumin as well as different transcription factors, and they give rise to the liver bud or hepatic diverticulum (in the fourth gestational week). The liver bud grows into the septum transversum and the cardiac mesoderm under the influence of GATA binding protein 6 (GATA6) and its target protein hematopoietically expressed homeobox (HHEX). These structures provide connective...
tissues to the developing liver and appropriate gene expression, which is regulated in a time-specific manner by liver-enriched transcription factors such as hepatocyte nuclear factor 6 (HNF6), required for normal development in the endoderm and mesoderm [1]. This process is termed “mesoderm inductive signaling” [2], and ß-catenin and wingless-related integration site (WNT) signaling play a crucial role in this pathway.

In this environment, cells from the liver bud form thick plates of hepatoblasts surrounding sinusoids fed from vitelline vessels derived from the wall of the yolk sac. The hepatic laminae initially consist of 5–7 cell layers, but by 5 months after birth the plates are two cells thick. The adult pattern of plates being one cell thick (Figure 1.1A) is not seen until at least 5 years of age [3]. The liver reaches a peak of relative size at the ninth gestational week, accounting for 10% of fetal weight, with the fetal liver being an important hematopoietic organ. In the healthy neonate, it represents up to about 5% of the body’s weight; during adolescence, this decreases to the final adult proportion of 2% of body weight, or a weight of around 1400 g in the female and 1800 g in the male.

**Vascular development**

The liver grows under the influence of its blood supply. Initially, blood is provided by the symmetrical vitelline veins, which ultimately join to form the portal vein. From the fifth week of gestation, the vitelline veins join the umbilical veins, and the liver is supplied with placental blood rich in oxygen and nutrients. In this time, the liver grows rapidly and reaches its peak size around the ninth gestational week. From the sixth week, the hematopoietic function of the liver is developed and the liver is the major hematopoietic organ until the fifth month of gestation, when the bone marrow takes over. The right umbilical vein then disappears, leaving the left umbilical vein as the principal supplier. Blood in the left umbilical vein takes one of three routes – supplying sinusoids on the left side of liver; supplying sinusoids on the right half of the liver via retrograde flow through a connection with the left branch of the portal vein; or supplying the inferior vena cava via the ductus venosus. Ultrasound studies in fetuses near term have shown that the left lobe receives almost exclusively nutrient-rich umbilical vein blood, whilst the right lobe only receives 50% of its supply from the umbilical vein, with the remaining 50% coming from the nutrient-poor portal vein. The left lobe is therefore significantly better perfused in utero, and is better able to withstand hypoxic insults. At birth, the left umbilical vein becomes the ligamentum teres and is replaced by the portal vein as the afferent venous vessel, and the ductus venosus becomes the ligamentum venosum. Hepatic artery branches appear later in development, emerging alongside the portal veins (Figure 1.2), first near the hilum and then toward the periphery deriving from the ductal plate. This spatial and temporal sequence mirrors that seen in the developing bile ducts. The artery appears before the definitive bile duct and is formed from portal constituents, specifically myofibroblasts.

**Biliary development**

The extra- and intrahepatic biliary systems develop from the endoderm as two independent subunits, merging at the end of the developmental process. The extrahepatic bile ducts and gallbladder develop from the pars cystica, the lower part of the hepatic diverticulum and its elongated stalk, as the duodenum withdraws from the septum transversum. The stalk develops behind the duodenum, the proximal part
becoming the ductus hepaticus, while the distal part is transformed to the ductus choledochus with its aperture in the duodenum.

Formation of the intrahepatic bile duct system begins around the eighth week of gestation. The periportal hepatoblasts become smaller and express cytokeratins (intermediate cytoskeletal components). This single-layer “sleeve” of epithelial cells surrounding the portal vein branch, with its associated mesenchyme, is the ductal plate (Figure 1.3) [4]. Some parts of the ductal plate are duplicated to a discontinuous second layer of cells around the first, resulting in a double layer around variable stretches of the portal perimeter. Within this double layer, slit-like lumens appear.

The early liver cells are bipotential, capable of differentiating into biliary epithelial cells or mature hepatocytes, a process that is started around the ninth gestational week and continues until after birth. The hepatoblasts destined to form ducts express biliary-type cytokeratins (CK19), identifiable by immunohistochemistry; while those differentiating into mature hepatocytes express different cytokeratins. The proximity to the portal vein endothelium and mesenchyme induces the differentiation toward biliary epithelium by substitution of hepatoblasts by cholangiocytes. The portal mesenchyme is important in inducing this differentiation as ductal plates do not form around the central veins. From 12 weeks’ gestation onward, the ductal plate is remodeled into individualized bile ducts. Both ductal plate development and its subsequent remodeling begin in the largest portal areas near the hilum and proceed outward toward the smaller portal tracts. During the migratory stage the tubular structures that have formed in the double-layered ductal plate become surrounded by portal mesenchyme and separated from the parenchyma. Connections are retained between the newly forming duct in the portal tract and the ductal plate and to the canaliculi (canals of Hering). The condition for a controlled development of the ducts is called “planar cell polarity” [6].

New studies suggest that remodeling does not happen by apoptosis, but by transformation of the ductal plate into periportal hepatocytes and hepatic progenitor cells [7]. Failure of the precise scheme of spatial and temporal remodeling leads to persistence of the ductal plate, known as “ductal plate malformation,” which can affect any caliber of portal tract. Periportal cells may retain the ability to differentiate toward bile duct epithelium, for instance the ductules that appear at the portal tract margins in biliary diseases. It is not clear whether these ductules originate from metaplasia of mature hepatocytes or biliary epithelial cells, or from progenitor cells located in the canals of Hering, possibly of bone marrow origin [8].

The integral membrane proteins of the JAGGED/NOTCH pathway have a crucial role in biliary development – a lack of Jagged1 (JAG1) results in malformation of the bile ducts, and mutations in the respective genes cause Alagille syndrome with biliary hypoplasia [9].

Extrahepatic biliary system development takes place before the intrahepatic bile duct formation begins. The extrahepatic bile ducts develop from the ventral foregut endoderm in proximity to the liver bud and the pancreatic bud. In contrast to the intrahepatic cholangiocytes, the extrahepatic biliary cells develop directly from the endoderm. Pancreatic and duodenal homeobox 1 (PDX1), hepatocyte nuclear factor 6 (HNF6), and Forkhead box protein F1 (FoxF1) play a role in the development, and the absence of the relevant genes leads to malformation.
Section 1: Understanding the Liver

The proliferation and development of the intrahepatic biliary system is not complete by 40 weeks of gestation, and bile duct genesis continues postpartum. The number of bile ducts per portal tract continues to increase and only reaches the adult ratio of a 1:1 pairing of hepatic arteries and bile ducts per portal tract at about 15 years of age.

Functional development of the liver and physiological adaptations at birth

The liver is the main site of hematopoiesis during gestation, starting at the sixth week, with a peak by the end of the first trimester, until the bone marrow becomes the main site at the end of the second trimester. New studies have shown that immature hematopoietic stem cells colonize the fetal liver and mature extravascularly, adjacent to the hepatocytes. It is normal to see evidence of residual hemopoiesis in the neonatal liver for some weeks after birth [10], but it is particularly prominent in neonatal hepatitis. Hemosiderin (as hemopoiesis decreases) and copper-associated protein accumulate in the liver and are deposited in periportal hepatocytes. Both are normal constituents of the neonatal liver and are not indicative of disease.

In utero, the placenta carries out most of the metabolic and detoxifying functions that normally take place in the liver, so hepatic enzymes such as glutamate dehydrogenase (GLDH), aspartate aminotransferase (ASAT), phosphoenolpyruvate carboxykinase (PEPCK), alanine aminotransferase (ALAT), and aldehyde dehydrogenase (ALDH) are rapidly induced at birth. Many conjugation reactions are mature by 2 weeks, but some uridine diphosphate (UDP)-glucuronyltransferase genes are not fully expressed for 2 years. The cytochrome P450 group and peroxisomal enzymes in the newborn function early (as in CYP 3A7) but others are delayed (e.g., CYP 1A2 and 3A4), so if the infant is unwell, acute phase proteins may have a long half-life because the immature liver is unable to clear them [10].

α-Fetoprotein, one of the main fetal serum proteins, is synthesized by fetal hepatocytes from 25–30 days after conception, and by the yolk sac and intestinal epithelium. Levels peak by the end of the first trimester but may exceed 100,000 ng/mL in healthy term newborns and only reaching normal adult levels around the first birthday. Albumin levels are close to adult levels at birth, but coagulation proteins and the activities of coagulation factors are low, increasing the risk of bleeding and hence the need for vitamin K administration at birth.

Bile acid synthesis starts at the fifth gestational week so that bile is secreted by the beginning of the second trimester. However, the change from placental to enteral nutrition at birth stimulates bile flow, bile acid secretion, and the enterohepatic circulation [3]. Gallbladder contraction is highly dependent on the maturity of the infant. γ-Glutamyltransferase, located at the canalicular surface of the hepatocytes, is slightly elevated in the serum in the first few months of life.

The immaturity of bile formation and the immaturity of the UDP-glucuronyltransferase enzymes lead to the development of physiological jaundice in neonates, while prematurity, hypoxia, sepsis, drug administration, or total parenteral nutrition may lead to cholestasis or hepatitis.

Term newborns have hepatic glycogen stores up to three times those of the adult liver, but these are quickly depleted, making the infants prone to hypoglycemia unless fed frequently before hepatic gluconeogenesis is induced.

The transition from umbilical venous to portal blood supply means that new substrates and bacteria are carried to the immature neonatal liver by the portal vein, exposing infants to infection.

Mature macroanatomy

The liver occupies most of the right upper quadrant of the abdomen under the diaphragm, nearly completely protected by the ribcage. Physical examination demarcates the borders of a normal liver in the midclavicular line, from the fifth intercostal space to just below the costal margin. In infants, a liver palpable below the right costal margin is normal. A normal liver span on percussion and palpation can be estimated as:

- <1 year: 4–5 cm.
- 1–5 years: 6–7 cm.
- 5–12 years: 8–9 cm.

A prominent left lobe that is palpable in the epigastrium may be normal in infants, but in older children is suggestive of pathology.

The macroscopic division of the liver into the right, left, quadrate, and caudate lobes does not correspond to the segmental division into eight (or nine, if segment IV is subdivided into IVa and IVb) segments (Figure 1.4). The right and left lobes of the liver are defined by the principal plane, or “Cantlie line” (named after the anatomist Sir James Cantlie, who was the first to accurately describe the division of the liver) [11]. The right and left halves of the liver are further subdivided into two sectors by the right and left fissures, which roughly correspond to the positions of the right and left hepatic veins [12]. The shape of the left lateral segment (segments II and III) varies greatly between a thin, “flatfish” lobe and a short, thick lobe (particularly segment III) or “blowfish” shape. This has particular relevance in monosegmental liver transplantation.

More important than the topographic description of macroscopically visible lobes is the segmental organization of the liver by the Couinaud system, which provides the basis for all major liver surgery, including liver transplantation. The caudate lobe is segment I, and the remainder of the segments are labeled according to their clockwise position. Each segment has its own independent vascular (apart from the liver veins) and biliary supply, which is surrounded by a fibrous sheath, an extension of the Glisson capsule.
Partial hepatectomies for tumor surgery or liver transplantation follow these segmental borders, achieving hemostasis in the residual liver instead of the traditional lobar macroanatomy [13].

**Figure 1.4** Segmental anatomy of the liver. (A) Dorsoposterior view of a normal adult liver. All segments can be seen only from this perspective. (B) Schematic view of the anterior aspect of a normal liver. The blood supply of segment IV is retrograde, which is of relevance in split liver techniques in liver transplantation. Segments II and III are also used for reduction hepatectomies and live-related donor transplantation. (From Baumann et al. [5].)

Partial hepatectomies for tumor surgery or liver transplantation follow these segmental borders, achieving hemostasis in the residual liver instead of the traditional lobar macroanatomy [13].

**Portal venous anatomy**
The portal vein is valveless and is a unique construction in the human body, being the third type of blood vessel supplying the liver. It drains blood from the splanchnic area and normally commences behind the neck of the pancreas as a cranial continuation of confluence of the superior mesenteric vein and the splenic vein, with a wide range of normal variants. The portal vein has two distinct muscle layers: a relatively thin, inner layer consisting of circular, smooth muscle cells, as in the normal media of a vein, and an outer layer of longitudinal muscle with abundant vasa vasorum – architecture resembling that of the gastrointestinal tract.

The portal vein branches extrahepatically at the hilum into a right and left portal vein; the latter supplies the caudate and quadrate lobes before it enters the parenchyma. The venous return from the gallbladder drains into the right branch of the portal vein. Each segment of the liver is supplied by its own branch of the portal vein. Anomalies of the portal vein are rare, but those most frequently seen are an abnormal position anterior to the head of the pancreas (typically associated with syndromic biliary atresia) and an abnormal communication with the inferior vena cava, resulting in a congenital portocaval shunt (Abernethy syndrome).

**Hepatic artery anatomy**
The arterial supply to the liver and biliary tree is notorious for variation in its origin and course relative to the surrounding anatomy, due to the complex embryological developmental of the celiac and superior mesenteric arteries. The hepatic artery usually originates from the celiac axis and divides into a right and left branch after the gastroduodenal artery has left the arteria hepatica communis (about 60% of cases). In about 25% of individuals, the right hepatic artery or an accessory artery arises from the superior mesenteric artery. In another quarter of individuals, the left lobe of the liver may be partially or completely supplied by an artery arising from the left gastric artery. Other less common anomalies are a very short common hepatic artery with long right and left arteries, with the gastroduodenal artery arising from the right hepatic artery or even arising separately from the celiac trunk.

The blood supply to the bile ducts is mainly arterial, although new studies have shown a portal venous contribution [14], and may be divided anatomically into hilar, supraduodenal, and pancreatic sections. The blood supply to the mid-portion of the common duct is axial, with a 3 o'clock and 9 o'clock positioned artery running alongside the duct, receiving an average of eight contributions from all of the surrounding named vessels. There is a 60% contribution from the gastroduodenal artery and 40% from the right hepatic artery. An additional supply to the supraduodenal duct is a consistent retroportal artery, arising from the celiac axis or superior mesenteric artery close to their origin from the aorta. These all form a plexus of vessels surrounding the bile ducts that extends into the liver. The ducts at the hilum receive blood from the right and left hepatic arteries and multiple small vessels that enter the caudate lobe. These vessels may be arranged in an arcade pattern, suggesting good collateral supply, or in a tree-like fashion from either the left or right hepatic arteries.

It is also important to note the frequency of segment IV arterial supply either from the right, proper, or left hepatic
artery, which has important implications for split liver transplantation. From corrosion-cast studies, it is obvious that a very important role for the hepatic arteries is the nourishment of the biliary system, and impairment of this blood supply will lead to ischemic consequences, with necrosis or stricture, while the liver parenchyma can survive by the oxygen provided by the portal vein supply.

Hepatic vein anatomy
The hepatic venous anatomy is relatively simple as there are three main hepatic veins, which lie above the portal structures within the liver, draining into the inferior vena cava (IVC). They divide the liver into sectors along an oblique plane; the middle hepatic vein separates the liver into right and left, while the left and the right hepatic veins divide the respective lobes into posterolateral and anteromedial sectors. The caudate lobe also has bilateral drainage with a relatively clear median plane, with direct venous channels into the IVC – these are more on the left, as this part of the caudate lobe is the larger and more consistent. The right hepatic vein may not be dominant, and much of the right posterior sector may drain into the IVC as a large accessory, caudally placed vein.

There are multiple other “dorsal” hepatic veins that drain directly into the IVC, which are thin-walled and fragile and require delicate ligation during right hepatectomy. The middle hepatic vein usually drains into the left hepatic vein within the liver substance, resulting in a common confluence, and receives branches from the right and left liver to a variable extent – mainly from segments V, IVb, and VIII. This venous drainage area becomes crucially important in liver-donor right liver transplants, as adequate drainage must be ensured for the donor (segment IV) as well as the graft (segments V and VIII) (Figure 1.4).

Biliary anatomy
The biliary system consists of both intra- and extrahepatic parts in which the interlobular or terminal bile ducts belong to the portal triad and have a diameter of <100 µm. The terminal bile ducts are accompanied by arterial vessels, which supply oxygenated blood to the bile ducts and also play a role in the immediate reabsorption of organic compounds from primary bile into the general circulation. Bile is then drained into the septal, segmental, and right or left hepatic ducts. The left hepatic duct drains segments II, III, and IV, and the right hepatic duct drains segments V, VI, VII, and VIII. Segment I, the caudate lobe, has its own biliary drainage. Variations of this are common, and in 78% of individuals the caudate lobe drains into both the left and right hepatic ducts. The left hepatic duct lies predominantly outside the liver parenchyma, and this can be used to advantage in dealing with more distal bile duct strictures. The right and left hepatic ducts join to form the common hepatic duct.

An important and common anomaly is for the right sectional (sectoral) duct to cross to the left and drain into the left hepatic duct. There is considerable variation in ductal anomalies. In about 70% of cases, there is a clear right–left confluence, and in 12% there is a trifurcation of the ducts at the porta hepatis [15], but many patterns of drainage are discernible. The right hepatic posterior and anterior sectoral ducts may drain separately at different levels or may join the left duct, as mentioned. A right posterior sectoral duct may join the hepatic duct as low as the insertion of the cystic duct or may even drain into the gallbladder.

The cystic duct drains the gallbladder and joins the hepatic duct in most cases at an acute angle on the right side. However, the level and type of insertion is variable and may be anterior or on the left, with a spiral or parallel configuration around the duct, and sometimes the cystic duct is joined with the right hepatic duct. The term “hepatocystic triangle” describes the inferolateral base, with the cystic duct and hepatic duct medially and the inferior surface of the liver superiorly. The length and diameter of the cystic duct also vary greatly – from 4 to 65 mm in length and from 3 to 9 mm in diameter.

The gallbladder lies on the anterior undersurface in the median plane between the two liver lobes. It is wrapped in the extension of Glisson’s capsule and may be embedded within the liver substance to a variable degree, or may even have a mesentery of its own.

The common bile duct, with a mean diameter of 6 mm and a length of 4–6 cm in adults, passes distally behind the duodenum and sometimes through the pancreas to reach its destination in the mid second part of the duodenum, the papilla duodeni major or papilla vateri, surrounded by sphincter muscle. At its terminal portion, it is joined by the pancreatic duct, with a short common channel in most cases. However, not infrequently, there may be pancreatico-biliary malunion with a long common channel, which is associated with choledochal dilation and cystic change due to pancreatic juice reflux (see the section on choledochal cysts in Chapter 25).

Malformation of the intra- and extrahepatic bile ducts is the major reason for chronic liver disease and liver transplantation in childhood.

Lymphatics
The lymphatic system of the liver consists of a deep and superficial part. Hepatic lymph is generated in the space of Disse, which is continuous with the lymph vessels. In the deep system, lymphatic vessels originate in the connective tissue spaces within the portal tracts and follow the arterial and portal vein branches toward the hepatic hilum. Superficially, lymphatics in the hepatic capsule drain to vessels either at the hilum or around the hepatic veins and IVC and eventually into the thoracic duct [16].
Microanatomy

Microanatomy is intimately related to function and is best considered by linking individual cellular constituents and their local relationships with function. Blood from the hepatic artery and portal vein needs to come into intimate contact with hepatocytes to allow the metabolism of dietary molecules and detoxification of compounds, and to distribute the diverse proteins synthesized by the liver. In order for the liver to fulfill its exocrine function, bile secreted into intercellular canaliculi has to find its way to the biliary duct system and ultimately to the intestine. These functions require a complex interaction between individual cells, as well as regulation of blood supply and innervation. The way in which groups of cells are organized into “functional units” has been the subject of much debate and is discussed further here.

Cellular constituents of the liver

The liver parenchyma consists of a number of different cell types. About 80% are hepatocytes, 10% are sinusoidal endothelial cells, 5% are lymphocytes, and 4% are Kupffer cells (hepatic macrophages), while biliary epithelial cells account for 1–3%.

Hepatocytes, arranged in branched and anastomosing cords, have a diameter of 25 µm with the nucleus in the center. In keeping with their diverse functions, the cytoplasm is rich in organelles, up to 1000 mitochondria in a single cell, with endoplasmic reticulum and a Golgi complex for protein production. Particulate glycogen forms much of the “background” of the cell. The hepatocytes have different surfaces or “domains” where they abut other hepatocytes, with which they communicate via gap junctions (lateral domain). The basal domain is where the hepatocyte contacts blood in the sinusoid, and the apical domain forms the connection to the bile canaliculus. The latter two domains are covered with microvilli, providing an enlarged surface area. The sinusoids are lined by a specialized endothelium, which has fenestrae (apertures) to facilitate the transfer of molecules and particles. The sinusoidal endothelium lacks a basement membrane, further facilitating exchange between the blood and hepatocyte.

Canaliculi only become visible on light microscopy in cholestatic disease (Figure 1.5). The canaliculus is demarcated from the sinusoids and the intercellular space by tight junctions. The 1–2 µm wide bile canaliculi constitute the outermost reaches of the biliary tree. They are interconnected and form a network of intercellular channels, which receive the bile secreted from hepatocytes. Actin and myosin filaments of the hepatocyte propel the bile into the canals of Hering (ductules or cholangioles) with the help of aquaporine-dependent and adenosine triphosphatase (ATPase)-dependent transporters, which are lined with a mixture of biliary epithelium and hepatocytes. They have a diameter of less than 15 µm and are located at the periphery of a portal triad.

Figure 1.5 Bile canaliculi formed by apical sides of hepatocytes in cholestatic liver disease. (A) Canaliculi in a child with neonatal cholestasis. The canaliculi are not visible in light microscopy in a normal liver. In this child with neonatal hepatitis, they are distended by bile plugs, making them prominent (arrows). (H&E, original magnification × 400.) (B) Electron microscopy of a canaliculus. The arrow shows granular bile in a canaliculus in a child on parenteral nutrition. There are microvilli lining the edge of the canaliculus.

Between the endothelial cells and the basal aspect of the hepatocytes lies the space of Disse (Figure 1.6). This is not normally visible with light microscopy, but can be seen if there is hepatic venous obstruction, and is easily seen on scanned electron microscopy (Figure 1.6B). The space of Disse is the source of lymph production and contains extracellular matrix components, including type IV collagen, laminin, and proteoglycans. This matrix interacts via adhesion molecules with the hepatocytes, modulates the cell phenotype and serves as a reservoir for cell growth factors, cytokines, and albumin, which are released by matrix degradation.
Hepatic stellate cells (previously known as Ito cells) are found in the space of Disse and produce extracellular matrix, cytokines, and growth factors, store vitamin A and lipid, and have fine extensions surrounding the sinusoids, possibly related to the control of vascular tone. When activated by liver injury, they transform into myofibroblasts and have an important role in fibrosis by secreting collagen into the space of Disse and hence obstructing oxygen exchange [17].

Kupffer cells are the central part of the phagocytic system of the liver. They are mostly found on the luminal side of the endothelial wall of the sinusoids, but they migrate to areas of injury or infection. In addition to phagocytic function, they are an important source of cytokine secretion. They have different phenotypes: the M1 phenotype is proinflammatory and the M2 phenotype supports healing and suppression of inflammation [18].

**Functional anatomy/regulation of blood supply**

The dual blood supply to the liver, by the hepatic artery and portal vein, is unique in the body. In resting conditions, the liver receives 800–1200 mL blood per minute accounting for a quarter of the cardiac output. About 25% of this hepatic inflow is oxygen-rich blood arriving via the hepatic artery; the remaining 75% is partially deoxygenated nutrient-loaded blood from the intestine, pancreas, gallbladder and spleen, supplied by the portal vein. Arterial and portal blood merges freely at the level of the sinusoids. Total blood flow into the liver varies considerably and is reduced during sympathetic stimulation or sleep. In contrast, portal blood flow increases following a meal; it is stimulated by a protein-rich feed, only moderately stimulated by carbohydrates, and there is little effect following lipids. The arterial blood supply is not determined by oxygen demand as half of the oxygen required is provided by the portal vein. Portal and arterial flow are closely related, and an experimental reduction of portal flow results in arterial hyperemia. This phenomenon is also known as the hepatic arterial buffer response (HABR) and becomes apparent in liver transplantation, when thrombosis of either the hepatic artery or the portal vein leads to compensatory flow rates in the other vessel.

About 20–25% of the normal liver consists of blood, 40% of which is situated in the large vessels and 60% in the sinusoids. As this is 10–15% of the body’s total blood volume, the liver serves as a reservoir with capacitance function. Liver blood volume can increase by hepatic venous pressure and may be tripled to about 60% in states of severe outflow obstruction. In hemorrhagic shock, in sympathetic stimulation, and in vascular dehydration, the liver can replace systemic volume rapidly.

Portal vein perfusion pressure is determined by the splanchnic arterioles and intrahepatic resistance and is approximately 6–10 mmHg. Arterial perfusion pressures depend on systemic perfusion pressures. The sinusoidal perfusion pressure is regulated by a number of factors in the afferent and efferent vessels, including muscular sphincter, autonomic nervous innervation, and paracrine function; it ranges between 2 and 4 mmHg.

The distribution of blood flow in the sinusoids is determined by variation in the size of the Kupffer and endothelial cells, which swell and shrink to control the patency of the sinusoidal lumen, while the stellate cells impair oxygen exchange by collagen synthesis in fibrosis.
Functional versus anatomical units

In the absence of explicit connective tissue septa delineating structural units, different models have been used to define the smallest functional unit in the liver (Figure 1.7):

- The **classic lobule (central venous lobule)**, hexagonal in shape, was described in 1833 [19]. It has a hepatic vein branch (“central vein”) at its center. Blood arriving in the portal tracts at the periphery of the hexagon feeds sinusoids around the whole of their circumference and hence different adjacent classic lobules, rather than all draining into the interior of the hexagon. It therefore has limited application as a functional primary unit.

- The **primary lobule**, described by Matsumoto et al. [20] uses the portal vein branches at the edges of adjacent central venous lobules to act as the center of the functional unit, giving rise to tortuous and branching three-dimensional units surrounding portal vein branches; it includes the classic lobule as a secondary structure [3, 15]. This model is based on actual vascular reconstruction (rather than the gelatin infusions used in the acinar concept) and is gaining widespread acceptance. Descriptive histology in the lobular model hence includes such terms as “centrilobular” hepatocytes (those around the central vein).

- The work of Rappaport et al. in 1954 defined the functional unit as an **acinus**, consisting of parts of two adjacent lobules [21]. The axis of the acinus is formed by the terminal branch of the portal vein, not visible in routine light microscopy. The three zones of the acinar concept corresponding to different levels of oxygen supply are illustrated in Figure 1.7. It should be noted that the three acinar zones do not equate to the regions described in the lobular concept. Acinar zone 3 is located around the center of the classic lobule, but not exclusively “perivenular,” and extends in an arc-like fashion from one portal tract to another. The acinar concept proved popular for pathologists as necrosis occurs first in the least well-oxygenated hepatocytes in a portal–central distribution, which corresponds to the most peripheral acinar regions (zone 3 in Figure 1.7), and not in the perivenular region.

However the functional unit is defined, the function of the hepatocytes, sinusoidal endothelium, Kupffer cells, and extracellular matrix composition varies between regions. “Periportal,” “perivenular,” and “midzonal” serve as useful descriptors for considering functional differences or gradients. Gene expression also shows a functional or a compartmental zonation [15]. The phenotypic variation may be determined by the declining gradient in oxygen concentration, the decreasing glucagon : insulin ratio, or other autocrine signals such as phosphoenolpyruvate carboxykinase (PCK) and carbamoylphosphate synthase (CPS). There are also compartment zonations, meaning that hepatocytes in a specific region express certain genes. Periportal hepatocytes are responsible for oxidative energy metabolism,

![Figure 1.7 Normal liver tissue. (A) Light microscopy of normal liver tissue. The small arrow points to the approximate outline of a classic hepatic lobule, centered around a central vein. In schematic diagrams this is often illustrated as a regular hexagon, with portal tracts at four points and “nodal points of mall” at the other two. This is rarely reproducible in practice, leading to the slightly irregular hexagon shown. The elliptical structure denotes postulated acinar zones 1, 2, and 3, centered around a terminal portal venule (not visible). This occupies portions of two adjacent classic lobules. The dotted rectangle shows the location of portal central bridging necrosis, which is observed in the clinical situation and which made the acinar concept popular from a pathological point of view. (H&E, original magnification × 40.) (B) Schematic view of the same anatomical and functional units of the liver. CV, central vein; PT, portal tract.]
such as gluconeogenesis, β-oxidation, and amino acid catabolism, bile formation, and cholesterol synthesis. Perivenous hepatocytes are involved in detoxification, glucose uptake for glycogen synthesis, glycolysis, lipogenesis, and ketogenesis. Periportal Kupffer cells are more active in phagocytosis than the centrilobular cells, which produce cytokines.

**Innervation**

The liver is innervated by afferent and efferent nerves of the autonomic nervous system, through sympathetic nerve fibers from the celiac ganglia and some parasympathetic input from the vagus nerve. Sympathetic nerve bundles accompany the large vessels and supply a dense perivascular plexus around the hilar blood vessels into the sinusoids, where nerves course in the space of Disse and surround isolated hepatocytes and stellate cells. Parasympathetic nerve fibers accompany the hepatic inflow system with ganglion cells close to the liver, forming a plexus around the hepatic artery and portal vein, but there is little cholinergic innervation beyond the portal tract.

The gap junctions may also provide direct electrical coupling between cells, bypassing the need for nervous innervation. Cholinergic stimuli increase metabolic activity, whereas adrenergic stimuli increase glucose mobilization into the blood. The realization that hepatic function is effective even in the denervated graft following liver transplantation has challenged longstanding views about the role of the autonomic nervous system in regulating metabolic activity in the liver.

Recent studies have shown that the glucose disposal effect of insulin and its negative effect on hepatic gluconeogenesis is significantly impaired by parasympathetic denervation. Furthermore, regulation of hepatic and muscle glucose uptake by portal vein glucose load does not function in a denervated liver. α-Adrenergic innervation is involved in hepatocyte replication and hepatic progenitor cells are activated by the vagal nerve [22].

**Function**

The liver is the central organ for metabolic homeostasis. Its main functions are:
- Regulation of uptake and processing of nutrients from the intestinal tract.
- Synthesis and biotransformation of proteins, carbohydrates, and lipids.
- Excretion of bile and elimination of hydrophobic compounds.
- Regulation of energy metabolism.
- Endocrine functions and mediation of normal growth and development.
- Immunological function.
- Drug metabolism.
- Regulation of fluid balance.

**Uptake and processing (synthesis, storage, and degradation) of proteins, carbohydrates, and lipids**

**Proteins**

The liver accounts for 15% of total body protein production, and the majority of these proteins are secreted as plasma proteins such as albumin (responsible for transport, keeping up osmotic pressure), other transport proteins such as ceruloplasmin, complement, protease inhibitors, and – clinically very important – coagulation and fibrinolytic proteins. Proteins are synthesized from dietary amino acids, and alanine and glutamine from muscle after transcription of protein-decoding genes into mRNA. Following translation and modification, proteins are secreted from the sinusoidal aspect of the hepatocytes into the circulation. Protein production is regulated by gene expression, protein synthesis, nutritional status, and hormone secretion. There is a higher production rate in acute illnesses – the acute phase response, in which C-reactive protein is the most commonly measured sign. Proteins are not stored in the liver, but amino acids are recycled to synthesize new molecules. The liver also plays a role in protein and glycoprotein degradation. Amino acid degradation takes place in the liver, generating the highly toxic metabolite ammonia, which crosses the blood–brain barrier readily and is associated with hepatic encephalopathy (see Chapters 9 and 18). The urea cycle, which is active in the liver, is largely responsible for its removal, and urea cycle defects present with severe encephalopathy (see Chapter 9).

**Carbohydrates**

The liver has a major role in maintaining blood glucose. Glucose, fructose, and galactose are taken up by the hepatocytes from portal blood. Glucose – in the fed state – is converted to glucose-6-phosphate by glucokinase and used as a precursor for glycogen synthesis by glycogen synthase and pyruvate via glycolysis, or else used in triglyceride production. Important hormones are insulin, which induces glycogen synthase and reduces gluconeogenesis and glucose output, FGF 15/19, which also stimulates glycogen synthesis, and glucagon, which stimulates gluconeogenesis and increases glucose output. Glucose is either released from glycogen by glycogenolysis mainly in short-term fasting periods or is synthesized from amino acids or substrates such as lactate or glycerol (gluconeogenesis) in long-lasting periods, regulated by the metabolic state and numerous transcription factors.

In conditions of stress or fasting, insulin and FGF 15/19 are downregulated, and therefore glucose uptake is reduced and glucose production is increased from glycogenolysis. Hypoglycemia is a sensitive test of liver function and is a sign of severe hepatic necrosis, indicating loss of liver function (see Chapters 9, 18, and 21). For the same reason, many infants with severe liver disease are unable to maintain their blood sugar levels during prolonged fasts.
Lipids

Lipid metabolism and lipogenesis are regulated by a complex interaction of hormones, such as insulin, and transcription factors but also by the metabolic state and circadian rhythm.

The liver is essential for cholesterol and lipoprotein metabolism. Dietary fat is absorbed in the small intestine by enterocytes and carried by chylomicrons, lipoprotein transport particles, from the intestine to the circulation and delivered as triglycerides to the peripheral tissues. The resulting cholestero-rich chylomicron releases non-esterified fatty acids which are taken up by the liver. The liver also synthesizes fatty acids from glucose in times of dietary excess, and these are subsequently stored as triglycerides, which are the principal source of energy, in lipid droplets in hepatocytes, or secreted as very-low-density lipoprotein (VLDL) particles. Fatty acids that are not converted to triglycerides or used in the synthesis of other molecules are used as energy supply by β-oxidation, and generate ketone bodies in the mitochondria, or in the case of very-long-chain fatty acids in the peroxisomes. Microvesicular steatosis in hepatocytes is a sign of mitochondrial or peroxisomal disease or drug toxicity (see Chapter 12).

Cholesterol is a component of all cell membranes and is essential for the production of steroid hormones and bile acids. The liver synthesizes cholesterol and fatty acids de novo from carbohydrates. Cholesterol homeostasis is controlled by uptake from lipoproteins and chylomicrons, which increase hepatic cholesterol, and by the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), which synthesizes cholesterol de novo. The amount synthesized in the liver is around 25% of the total amount synthesized and twice that absorbed from the diet. In the liver, cholesterol is either “free” or stored as cholesterol ester. The degradation of cholesterol also takes place in the liver through the oxidation to bile acids and biliary excretion of cholesterol. Cholesterol may crystallize in the gallbladder and forms part of most gallstones. A number of cholestatic liver diseases (e.g., biliary atresia or Alagille syndrome) lead to elevated plasma cholesterol due to deficient biliary excretion and catabolism.

VLDLs are the main lipoproteins secreted by the liver and carry triglyceride and cholesterol to other tissues, where they are converted to low-density lipoproteins (LDLs) and then to free fatty acids. High-density lipoproteins (HDLs) carry cholesterol from the peripheral tissues back to the liver. Fatty liver occurs when the synthesis of triglycerides exceeds the liver’s capacity for export or internal metabolism [23].

Bile and bile acids

The production and excretion of bile is an elemental function of the liver, ensuring the elimination of unwanted internal and external metabolites and lipid absorption. Bile is produced in hepatocytes (75%) and cholangiocytes (25%), is further modified in the bile ducts, and is concentrated in the gallbladder. In adults, about 600 mL of isotonic watery bile with a pH of 7.8 is produced daily in order to facilitate the excretion of many compounds, including drugs, toxins, and waste products as well as cholesterol and bilirubin, and to provide bile salts to the intestine for the emulsification and absorption of dietary lipids and fat-soluble vitamins. Bile formation is an osmotic process driven by the excretion of organic metabolites (mainly bile acids) and the influx of electrolytes and water. It is traditionally divided into “bile salt dependent” (the relationship of canalicular bile flow to bile salt excretion) and “bile salt independent” (the active secretion of electrolytes and other solutes, mainly glutathione).

The main components of bile besides water are bile acids (12%), phospholipids (4%), cholesterol (0.7%), and conjugated bilirubin (0.1%). Lecithin increases the solubility of cholesterol in bile by micelle formation exponentially to allow a 10-fold concentration of bile acids and cholesterol after concentration by the gallbladder. The main electrolyte in the bile is sodium at a concentration of 280 mmol/L; other electrolytes and bicarbonate are less concentrated, or unchanged. The primary bile acids – cholic acid and chenodeoxycholic acid – are synthesized from cholesterol by 7α-hydroxylation and subsequently conjugated with taurine and glycine to facilitate secretion.

Primary bile salts are transformed by intestinal bacteria into secondary bile salts – cholic acid into deoxycholic acid and chenodeoxycholic acid into lithocholic acid and subsequently to ursodeoxycholic acid (UDCA). They are reabsorbed in the ileum and returned to the liver via the portal vein and are the major stimulus for bile secretion. In normal conditions, UDCA represents only 3% of the bile salt pool. It is more hydrophilic than the other bile salts and is used therapeutically to stimulate bile secretion; it may prevent the hepatocytes from damage caused by hydrophobic bile salts. In chronic liver disease, this balance is shifted to a predominant production of chenodeoxycholic acid, which lowers the bile pH.

Hepatic bile formation and the biliary excretory function are closely related. In adults, the enterohepatic circulation of bile salts occurs 4–12 times in 24 h, enabling the body to retain most of the 5–6 g in the body bile salt pool, as the total stock of bile salts is not sufficient for fat absorption. Neonates have about half the bile salt pool of an adult, and ileal bile salt reabsorption is lower. Their intestinal bile acid concentration may be low, leading to poor micelle formation and reduced uptake of fat-soluble vitamins and dietary lipid in comparison with older children and adults. Although this is rarely a cause of malnutrition and/or steatorrhea, it needs to be considered in cholestatic conditions when early supplementation of fat-soluble vitamins is indicated. Bile acid uptake from portal blood is physiologically lower in neonates in comparison with older children, and elevated levels of bile acids may be mistaken for cholestatic liver disease.

Intrahepatic and extrahepatic bile salt transport

The transport processes for bile salts are complex and quite efficient, as 95% of the excreted bile salts are recycled from the enterohepatic circulation. The polarized hepatocytes
The liver is the main organ of the body for the metabolism of energy and nutrients. The liver plays a central role in maintaining blood glucose homeostasis at constant levels. The liver is responsible for the disposal of around two-thirds of the oral glucose load, divided into uptake and downregulation of glucose release, so absorbed glucose is taken up into peripheral tissue. Hepatic and extrahepatic uptake of glucose are controlled by the load of glucose in the portal vein blood. The glucostat function of the liver is achieved by controlling the storage and release of glucose from glycogen, followed by glycolysis and gluconeogenesis.

**Regulation of energy metabolism**

The energy metabolism of the body is integrated by the liver through glucose metabolism and fatty acid oxidation. The liver has a central role in maintaining blood glucose homeostasis at constant levels. The liver is responsible for the disposal of around two-thirds of the oral glucose load, divided into uptake and downregulation of glucose release, so absorbed glucose is taken up into peripheral tissue. Hepatic and extrahepatic uptake of glucose are controlled by the load of glucose in the portal vein blood. The glucostat function of the liver is achieved by controlling the storage and release of glucose from glycogen, followed by glycolysis and gluconeogenesis.

Excretion of bilirubin

As well as its role in facilitating bile salt homeostasis, the biliary system also serves as the primary pathway for eliminating bilirubin, excess cholesterol, and hydrophobic xenobiotics. Bilirubin is a toxic degradation product, 80% of which is derived from the breakdown of erythrocytes; the remainder stems from heme-containing myoglobin, cytochromes, or failed erythropoiesis. Mononuclear phagocytic cells oxidize heme to form biliverdin, which is then reduced to unconjugated bilirubin. This unconjugated bilirubin is usually albumin-bound, but – when exceeding the binding capacity of the albumin – it can diffuse across the blood–brain barrier and cause kernicterus in neonates.

The albumin-bound bilirubin is transported to the hepatic sinusoids, is actively transported into the hepatocytes via the basolateral membrane with the contribution of OATP-1B, and bound to ligandin in the cytoplasm is transported to the endoplasmatic reticulum.

The enzyme UDP glucuronyltransferase (UGT1A1) catalyzes the conjugation of bilirubin with one or two molecules of glucuronic acid in the endoplasmic reticulum, and the conjugated or direct bilirubin is excreted with the help of Mrp2 as hydrophilic bilirubin glucuronides via the canalicular membrane. Some may be secreted to the sinusoids and, following intestinal excretion, bacterial β-glucuronidases degrade most of these bilirubin glucuronides to colorless urobilinogen, which is reduced to stercobilin, accounting for the brownish color of feces. About 20% of urobilinogen is reabsorbed in the ileum and colon and returned to the liver via the portal vein and excreted into the urinary tract.

UGT1A1 belongs to the UGT family of conjugating enzymes, which are expressed in a wide range of tissues and which catalyze glucuronidation of various substrates, including steroid hormones, carcinogens, and drugs. UGT1A1 activity in the first days after birth is below 10% of adult activity, contributing to physiological neonatal jaundice. Mutations in the UGT1A1 gene either reduce the activity of UGT1A1 toward bilirubin or reduce enzyme activity. Complete absence of UGT1A1 activity causes Crigler–Najjar syndrome type 1 presenting with severe hyperbilirubinemia, and a significant reduction of activity causes Crigler–Najjar syndrome type 2. A very mild reduction of UGT1A1 activity by missense mutation or reduced expression of the enzyme is present in 6% of the general population, causing Gilbert syndrome with its characteristic mild elevation of unconjugated bilirubin (see Chapter 8).

**Excretion of bile salts across the canalicular plasma membrane**

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genesis in long episodes of fasting. The glycogen content of a liver of a 10 kg child is around 20–25 g, increasing to about 100 g (55–72 mg glycogen per gram of liver tissue) in an adult. Studies have shown that increased glycogen content is associated with impaired hepatic insulin signaling and glycogenesis. As the normal resting glucose requirement is between 4 and 6 mg/kg/min, the glycogen stores last for less than a day of fasting, after which gluconeogenesis is activated. In prolonged fasting, total body glucose requirements decrease from 160 to 40 g glucose/day after 5–6 weeks of starvation. The healthy body can tolerate this, because fatty acid oxidation becomes the main source of fuel for respiration. Glucose uptake into the hepatocyte is insulin independent, via glycogen phosphorylase and glycogen synthase, and has a direct regulatory effect on glycogen synthesis and the storage and release of glucagon and adrenaline.

The liver acquires fatty acids from the blood, from chylomicron remnants, and by de novo synthesis. Its triglyceride content correlates with visceral fat content. The conversion of excess glucose to fatty acids only takes place when hepatic glycogen stores are complete. Fatty acids are esterified to triglycerides and exported from the liver as VLDLs. Triglycerides in VLDLs from the liver and from the intestinal absorption of lipids are hydrolyzed by lipoprotein lipase and taken up in the peripheral tissues, where fatty acids are metabolized for energy or stored [23].

**Endocrine function**

The liver plays an active role in endocrine regulation. In response to pituitary growth hormone activation, the liver produces the majority of the circulating mitosis-inducing (mitogenic) polypeptide hormones insulin-like growth factor 1 and 2 (IGF-1 and IGF-2). These have anabolic and metabolic effects, regulate the proliferation of various cells, and are crucial in growth and development leading to failure to thrive in chronic liver disease. IGF-1 may therefore be used as a marker of hepatocellular dysfunction. The specific endocrine effect of IGFs and other hormones, such as steroid hormones, is modulated by different binding proteins (IGF-binding proteins 1–6, sex hormone-binding globulin, or thyroid-binding globulin) that are synthesized in the liver. These binding proteins transport the hormones, regulate their metabolic clearance, and directly modulate hormone interactions with specific receptors. Angiotensinogen (important in the renin–angiotensin–aldosterone system for blood pressure regulation) and thrombopoietin (stimulating megakaryopoiesis) are also synthesized by the liver. These binding proteins transport the hormones, regulate their metabolic clearance, and directly modulate hormone interactions with specific receptors. Angiotensinogen is an important in the renin–angiotensin–aldosterone system for blood pressure regulation and thrombopoietin (stimulating megakaryopoiesis) are also synthesized by the liver. Thyrroxine (T₄) is converted into the metabolically active form of T₃ in the liver by iodothyronine deiodinase, which accounts for the low T₃ syndrome in patients with decompensated cirrhosis. Adrenocortical dysfunction is known to frequently occur in liver disease [26]. Hormonal dysfunction in liver disease may develop from a reduced clearance of hormones (e.g., gynecomastia in men), from portosystemic shunting, dysregulated synthesis of binding proteins, or impaired endorgan sensitivity to the hormone (i.e., insulin resistance in cirrhosis).

**Immunological function**

Lymphocytes enter the liver through the sinusoids and the space of Disse. The liver contains approximately $10^{10}$ lymphocytes, both of the adaptive immune system (predominantly T cells and a smaller amount of B cells), which require previous exposure to antigen for efficacy, and of the innate immune system (natural killer (NK) cells). The liver also contains NK T cells that express both T-cell and NK-cell markers, which play a role in the clearance function of the liver in filtering gut-derived endotoxins and microorganisms. Activated cluster of differentiation 8 (CD8) T cells (effector cells) induce and maintain the immune reaction to hepatotropic pathogens. In liver injury, inflammatory and anti-inflammatory response is mediated by hepatic NK cells.

The liver contains three types of antigen-presenting cells: Kupffer cells, liver sinusoidal endothelial cells (LSECs) and dendritic cells. Kupffer cells are macrophages derived from monocytes that are important in the first line of clearing toxins, viruses, and bacteria from the portal vein blood and initiate the immune response by cytokine release (tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), IL-10) and antigen presentation (they are conspicuous in acute hepatitis). Following liver transplantation, donor Kupffer cells are rapidly (within days) replaced by recipient Kupffer cells infiltrating the liver. LSECs – as their name suggests – are lined around sinusoids, whereas dendritic cells in the liver usually surround central veins and portal tracts; both are efficient in antigen processing and presenting (see Chapter 3) [27].

**Drug metabolism (xenobiotic metabolism)**

The liver is the prime site for drug metabolism in the body, as most of the xenobiotics are absorbed by the gastrointestinal tract and reach the liver via the portal vein. Most drugs are transported into the hepatocytes by ATP-dependent solute carriers and are metabolized in the smooth endoplasmatic reticulum of the hepatocytes. During the first phase, enzymes (mainly of the cytochrome P450 family) change the xenobiotic structure mostly by oxidation, and rarely by reduction or other reactions. Reactive oxygen species that are toxic to the cell are generated during this process and require a range of antioxidant mechanisms (molecules (e.g., glutathione and vitamin E) and enzymes (e.g., superoxide dismutase)) to render them inert. Thus, CYP3A4, the most important member of the P450 group, is expressed in zone 3. The metabolized drug, which may itself be toxic, enters the second phase of metabolism: the conjugation with hydrophilic compounds (e.g., glucuronic acid or glutathione) to increase the water solubility and the detoxification of toxic molecules produced in the first phase of drug metabolism.
Once rendered hydrophilic, the drug metabolite is either further metabolized or directly excreted via the kidneys or the bile. There are individual differences in drug metabolism, and the enzymes responsible for drug metabolism may be either induced or inhibited by other drugs or chemicals. Severe liver failure reduces the ability to metabolize drugs, so that drug effects are prolonged (e.g., sedatives or anesthetic agents), or there may be an accumulation of toxic metabolites, which complicates hepatic encephalopathy (see Chapter 12).

**Liver function in maintaining fluid balance**

The liver can retain and release a significant volume of whole blood and/or plasma and hence influences the circulating blood volume. Although the direct interaction between the liver and kidney is not fully understood, impaired liver function leads to a reduced ability to excrete sodium and water leading to hepatorenal syndrome with renal failure. A number of factors are involved, which include: hyperaldosteronism and/or increased tubular sensitivity to aldosteronism, and increased renal sympathetic nerve activity. The hepatorenal syndrome is caused by reduced renal perfusion, renal vasoconstriction, cardiac dysfunction, and release of cytokines. Portal hypertension may precipitate the hepatorenal reflex to activation of the renin–angiotensin–aldosterone system and the release of antiuretic hormone [28]. Splanchnic vasodilation is probably an initial adverse event that leads to renal vasoconstriction, followed by a reduction of renal blood flow and of the glomerular filtration rate. Sodium retention is the first sign of renal dysfunction, followed by water retention, leading to dilutional hyponatremia in plasma. Plasma volume expansion due to sodium and water retention, together with sinusoidal hypertension (portal pressure gradient of >12%), is a key factor in the pathogenesis of cirrhotic ascites (see Chapter 21).

**Liver growth and regeneration**

The expected lifespan of a hepatocyte is about 200–500 days. Even though the liver is more stable in adulthood, the liver cell mass remains highly flexible and varies throughout life, depending on metabolic demands such as disease or pregnancy. In normal children and adults, hepatic regeneration occurs by replication of mature hepatocytes, cholangiocytes, and endothelial cells and the liver can recover from mild injury completely. This process can be upregulated – for instance, following trauma or partial hepatectomy – and the liver can be reconstituted by proliferation of mature hepatocytes within days and weeks.

Liver regeneration is also reliant on hepatic progenitor cells. Pluripotent, so-called oval cells, that are located in the canals of Hering, are stimulated by injury and differentiate into hepatocytes and/or cholangiocytes. It is not known whether the recruitment of hepatic progenitor cells from bone marrow stem cells is a significant part of liver regeneration.

The finding of the hematopoietic stem cell marker and proto-oncogene c-kit in certain biliary cells from diseased pediatric liver was one of the first steps in demonstrating the presence of stem cells in humans [29]. Theise et al. [8] demonstrated the presence of Y chromosome-positive hepatocytes and biliary epithelium in female recipients of a therapeutic bone marrow transplant from male donors, confirming the ability of human bone marrow–derived stem cells to differentiate into the hepatic cell lineages.

Liver regeneration varies with circadian rhythms and metabolic requirements. Increased metabolic demands and pro-inflammatory cytokines are essential. Cytokines (TNF-α, interferon-γ, IL-6) and growth factors (hepatocyte growth factor) initiate liver regeneration by activating hepatocyte replication and hepatic progenitor cells. The degradation of extracellular matrix by metalloproteinases to release growth factors is an essential step in hepatocyte proliferation; on the other hand, the loss of certain metalloproteinase inhibitors leads to liver failure.

Hepatocyte transplantation and hepatic stem cell therapy have been studied widely over the last years but have not (yet) proven to be equivalent to liver transplantation.

**Liver fibrosis**

The outcome of most chronic disease processes in the liver is fibrosis. In hepatic fibrogenesis, the activation of stellate cells by injured hepatocytes, biliary cells, or Kupffer cell secretion leads to the conversion of quiescent vitamin A- and fat-storing cells into proliferative, contractile, and fibrogenic myofibroblasts. These cells produce an excess of type I and III collagen, which replaces the normal extracellular matrix in the portal tracts and lobules and leads to fibrous septal tracts and obstruction of the space of Disse. Liver fibrosis is a partially reversible process, even though complete restitution remains debatable. Different metalloproteinases that cleave collagens are mainly involved in matrix degradation of the liver, although neutrophils, macrophages, and stellate cells also contribute to this process. Tissue inhibitors of matrix metalloproteinases (TIMPs) are the key regulators in determining the reversal of fibrosis. Sustained TIMP-1 expression inhibits protease activity for matrix degradation and blocks apoptosis of activated stellate cells. Furthermore, soluble mediators such as transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF), and fibroblast growth factors may regulate fibrogenesis by influencing stellate cells and are the subject of further studies of pharmacological intervention [30].