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ESSENTIALS Liver and biliary tract The liver, sited in the right upper quadrant of the abdomen, comprises eight segments, each of which is a complete functional unit with a single portal pedicle and a hepatic vein. Within the functional segments, the structural unit is the hepatic lobule, a polyhedron sur- rounded by four to six portal tracts containing hepatic arterial and portal venous branches from which blood perfuses through sinus- oids, surrounded by walls of hepatocytes that are a single cell thick and lined by specialized endothelial cells with ‘windows’ (fenestrae), to the centrilobular region and the central hepatic veins. Bile se- creted through the canalicular membrane of the hepatocyte collects in biliary canaliculi, from which it passes through the biliary tract into the gut. The liver secretes bile, which aids digestion by emulsifying lipids, and has a central role in metabolism of (1) bilirubin, from haem; (2) bile salts, the principal mechanism for clearance of cholesterol; (3) carbohydrates; (4) amino acids and ammonia; (5) proteins, most circulating plasma proteins being produced by hepatocytes; and (6) lipid and lipoproteins. Pancreas The pancreas lies in the retroperitoneum and is composed of (1) an exocrine portion centred on acini, producing an alkaline secretion containing digestive enzymes including serine prote- ases, exopeptidases, and lipolytic enzymes, draining through a ductal system into the duodenum; and (2) the islets of Langerhans, which secrete insulin (also glucagon, somatostatin, and pancreatic polypeptide). Liver and biliary tract The hepatic diverticulum originates from the foregut (duodenum) at week 3 to 4 of gestation and then subdivides into hepatic and biliary buds. The hepatic bud contains bipotential progenitor cells that differentiate into hepatocytes and biliary cells. Liver structure is produced by progressive subdivisions of the hepatic bud. The biliary bud forms the gallbladder. Ingrowing capillary plexuses ultimately form sinusoids. Kupffer cells derive from circulating macrophages and stellate cells from submesothelial cells located beneath the surface of the developing liver. The adult liver weighs 1.2 to 1.5 kg and has a highly vascular architecture. The classic descriptions of liver anatomy demonstrating the complexity of different

parenchymal and nonparenchymal elements have a long history, but only recently have they been united with an increasing understanding of the intricate functional organization and physiological compartmentalization of liver structure. This has had a profound effect on our understanding of the control of physiological processes and the development of liver surgery. A grasp of the hepatic anatomy is key to an appreciation of these complex functional arrangements. Morphological anatomy This describes the classic structure of the liver into two lobes, right and left, and the accompanying vascular structures, lymphatics, and biliary tract (Fig. 15.20.1). The liver, situated in the right upper quadrant of the abdomen, is covered by Glisson's capsule, a visceral continuation of the peri- toneum. Three ligaments attach to surrounding structures—the falciform ligament anterior and superiorly, and the two posterior triangular ligaments which enclose the retrohepatic vena cava and the small bare area of the liver. Inferiorly, Glisson's capsule attaches to the lesser curve of the stomach and at the hepatic hilus encases the hepatic pedicle consisting of hepatic artery, portal vein, and common hepatic bile duct. Hepatic lobes The two major lobes, right and left, and two accessory lobes, quadrate and caudate, are defined by points of surface anatomy. The larger right lobe comprises the dome of the liver under the diaphragm and is limited anteriorly and medially by the falciform ligament and posteriorly by the right border of the inferior vena cava. The quadrate lobe inferiorly abuts on to the antrum of the stomach and first part of the duodenum and is bor- dered by the posterior transverse hilar fissure, the gallbladder 15.20 Structure and function of the liver,
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 fossa laterally, and the umbilical fissure medially. The caudate lobe lies posterior and superior to the quadrate lobe limited by the vena cava and the ligamentum venosum. Finally, the left lobe has the umbilical fissure medially and the falciform ligament anteriorly. Vascular anatomy The portal vein, hepatic duct, and hepatic artery form the hep- atic pedicle with the bile duct anterior in the free edge of the lesser omentum and the portal vein posteriorly (Fig. 15.20.1c). The latter is formed by the confluence of the superior mesenteric vein and the splenic veins running posteriorly in the pedicle, dividing into left and right branches to supply each lobe (Fig. 15.20.2). The left gas- tric vein also drains into the portal vein and may, in the presence of portal hypertension, be a major feeding vessel for gastro-oesophageal varices. The portal vein is anatomically unique as it drains into the liver, not the heart. The hepatic artery arises from the coeliac axis as the common hepatic artery before dividing into a gastroduodenal and the main hepatic artery. There are several common anatomical vari- ants of the arterial supply of the liver, which are of no functional significance but which are of importance in liver transplantation and during surgical resection. The standard division into single left and right hepatic arteries is present in approximately 70% of cases (Figs. 15.20.1c and 15.20.2), but common variants include a separate second right hepatic artery (10%), separate right and left hepatic arteries (8%), and origin of the main hepatic artery off the superior mesenteric artery (2.5%). Variants of the left hepatic (a) Orientation Liver Oesophagus Stomach Spleen Pancreas Colon Rectum Appendix Large bowel Biliary tree Duodenum Jejunum Ileum Anus Small bowel

Umbilical fissure Inferior view Anterior view Superior view Right lobe (b) Caudate lobe Right triangular ligament Porta hepatis Inferior vena cava Ligamentum venosum Left lobe Gallbladder fossa Falciform ligament Left lobe Inferior vena cava Right lobe Right triangular ligament Left triangular ligament Right triangular ligament Left triangular ligament IVC Bare area Right lobe Coronary ligament Falciform ligament Left lobe Caudate lobe Right hepatic duct (c) Cystic artery

Cystic duct Gallbladder Common bile duct Accessory duct of Santorini Ampulla of Vater Superior mesenteric vein Pancreatic duct Splenic vein Gastroduodenal artery Common hepatic artery Left gastric vein Left hepatic duct Pancreas Duodenum Fig. 15.20.1 (a) Orientation of the liver; (b) lobar anatomy and relations of the liver; (c) hilar, portal biliary tract, and pancreatic anatomy.

section 15 Gastroenterological disorders 3034 arterial supply also occur, with a separate left hepatic artery arising from the left gastric artery in 10% of cases. Venous drainage of the liver is through the three main hepatic veins, right, left, and middle, the latter two coalescing before joining the inferior vena cava. The caudate lobe drains separately through an array of small spigelian veins directly into the inferior vena cava. The functional anatomy of the liver (see ‘Functional anatomy) de- scribes the relationship between the main divisions of the portal vein and their draining hepatic veins running in the right, left, and main scissures (Fig. 15.20.3). Biliary anatomy Biliary canaliculi drain into left and right hepatic bile ducts forming the common hepatic duct until entry of the cystic duct, after which it is designated the common bile duct and has a diameter of less than 8 mm. The left hepatic duct follows a nearly horizontal course, par- tially extrahepatic. Anatomical variants are again quite frequent, and are surgically important, the most common being drainage of the cystic duct directly into the right hepatic duct. The common bile duct passes behind the first part of the duodenum, through pancre- atic tissue to the ampulla of Vater, joining drainage of the pancreatic duct (Fig. 15.20.1c). The gallbladder lies in a shallow depression in the underside of the liver, may contain up to 50 ml of bile, and is con- nected to the cystic duct with a spiral valve. Lymphatics The liver has a high blood flow (25% of cardiac output) and a highly permeable microcirculation. The consequent production of intersti- tial fluid, intrahepatic lymph, is formed in the perisinusoidal space of Disse between the hepatocytes and sinusoidal lining endothe- lium. Lymphatic vessels drain via the portal tracts, closely applied to the hepatic arterial branches, to the hilum and thence to the thor- acic duct. A smaller proportion drains with the hepatic veins and some interstitial fluid drains through Glisson’s capsule into the peri- toneum. Lymph flow acts to drain from the liver the interstitial fluid and protein that forms inevitably through microvascular filtration. The lymph flow rate in mammalian liver is approximately 0.5 ml/ kg of liver per minute, making up 25 to 50% of thoracic duct lymph flow, and may be increased either by elevated microvascular pressure (hydrostatic pressure) through increased hepatic venous pressure or increased inflow pressure, or by reduced transcapillary oncotic pressure. Nervous system Both sympathetic and parasympathetic efferent innervation of the liver are described, an anterior plexus around the hepatic artery and posterior plexus around the portal vein. Sympathetic stimulation increases glucose release and glycogenolysis, and reduces oxygen consumption, ammonia uptake, and bile formation. Hepatic vas- cular resistance also rises as does portal pressure and there is rapid expulsion of blood out of the liver into the systemic circulation. An intrinsic nervous system with a wide variety of neurotransmitters, including noradrenaline, prostanoids, neuropeptide Y, substance P, and vasoactive intestinal peptide, is closely located to smooth muscle cells, fibroblasts, endothelial lining cells, and biliary epithe- lium within the liver and may be involved in chemoreception and osmoreception. Extrinsic nervous regulation of hepatic physiological processes seems to be of minor importance as there is no apparent impair- ment of liver metabolism or bile formation following orthotopic liver transplantation. It may be more relevant during pathophysio- logical stress: the existence of a hepatorenal reflex in patients with cirrhosis has been postulated whereby an increase in sinusoidal pressure is associated with increased efferent renal sympathetic ac- tivity and reduced renal blood flow. In animal models of chronic liver disease, the metabolic consequences of sympathetic nerve

stimulation are impaired but the haemodynamic responses are exaggerated. Venous anatomy Arterial anatomy VENOUS OUTFLOW: VENOUS INFLOW: right, middle and left hepatic veins into IVC PORTAL VEIN Liver middle colic right colic ileocaecal site of portosystemic anastomosis - lower oesophagus, anal canal, bare area of liver, spleen - also periumbilical and retroperitoneal Aorta Coeliac trunk Superior mesenteric artery

- Variant right accessory hepatic artery
- Left gastric
- Splenic
- common hepatic
- Right gastric
- Gastroduodenal
- Hepatic with left and right branches Common hepatic artery left colic inferior mesenteric splenic right gastric left gastric (with oesophageal branches) superior rectal Variant left accessory artery Fig. 15.20.2 The venous and arterial anatomy of the liver. 1 2 3 4 5 6 7 8 Fig. 15.20.3 Functional anatomy of the liver with Couinaud's segments.

15.20 Structure and function of the liver, biliary tract, and pancreas 3035 Functional anatomy Following the initial descriptions by Cantlie in 1898, there has been an increasing appreciation of the importance of the functional anatomy of the liver, the culmination of which was the description by Couinaud of the present eight liver segments that underpins all modern hepatic surgery. Each segment is a complete functional unit with a single portal pedicle and a hepatic vein (Fig. 15.20.3). There are four portal pedicles, two for each lobe, each supplying a sector of the liver, divided from each other by the three hepatic veins lying in a right, middle, and left scissure. This separates the liver into a right and left liver, different from lobes, with inde- pendent vascular supply and biliary drainage. Within each sector of the liver there are further subdivisions into segments. The caudate lobe (segment 1) has its own venous drainage, manifest during the Budd–Chiari syndrome with thrombosis of hepatic veins when all venous drainage attempts to pass through this segment with conse- quent lobar hypertrophy. The left liver consists of the left posterior sector of segment 2 alone, and a left anterior sector of segment 3 medially and segment 4 laterally separated by the umbilical fissure. The right liver comprises a posterior sector of segment 7 superiorly and segment 6 inferiorly and an anterior sector of segment 5 inferiorly and segment 8, being most of the dome of the liver, superiorly. Structural organization Within the functional segments of the liver, the structural unit is the hepatic lobule, a polyhedron (2 × 0.7 mm) surrounded by four to six portal tracts containing hepatic arterial and portal venous branches from which blood perfuses through sinusoids, surrounded by walls of hepatocytes that are a single cell thick and lined by specialized endothelial cells with 'windows' (fenestrae), to the centrilobular re- gion and the central hepatic veins (Fig. 15.20.4). The portal vein branches give off numerous terminal portal ven- ules that run around the lobules in the interlobular septa accom- panied by arterioles and bile ductules, and subsequently branch into inlet venules which each supply a hepatic microcirculatory subunit consisting at the base of numerous interconnected sinusoids and, at the apex, the central vein (Fig. 15.20.4). Sinusoids Sinusoids are specialized capillaries without a basement membrane and lined with endothelial lining cells through which proteins of low molecular weight may percolate into the space of Disse. The sinusoidal membrane of the surrounding hepatocytes is covered by microvilli that increase the surface area sixfold (Fig. 15.20.5). Within the sinusoids, Kupffer cells and liver-associated lympho- cytes may be found, and within the space of Disse, the hepatic Hepatic vein

Input to portal tracts (from portal vein: blue, hepatic artery: red) and output from portal tract (to biliary tree: green) Central vein (drains to hepatic vein) Sinusoids Hepatocytes Biliary canaliculus Lobules Central veins Portal tracts Lobule Inlet venule Central vein Portal vein Terminal portal vein Hepatic microcirculatory subunit Fig. 15.20.4 Liver microanatomy. Arterial and venous blood mixes in sinuosoids and flows to a central vein, which sits in the centre of a hexagonal lobule and ultimately supplies the corresponding hepatic vein. Bile flows in the opposite direction to blood along canaliculi that form biliary ductules, which make up portal triads along with the hepatic arterial and portal venous branches.

section 15 Gastroenterological disorders 3036 stellate cells (also called Ito, fat storage, or perisinusoidal cells), which respectively make up 2%, 0.2%, and 1.4% of the lobular par- enchyma (Table 15.20.1). Biliary canaliculi Bile secreted through the canalicular membrane of the hepatocyte collects in biliary canaliculi, which pass around hepatocytes until draining through the short canal of Hering into the bile ductule. Cholangioles are lined by three or four cells that eventually become cuboidal epithelium. The volume and flow rate of bile are low; secretion into the duo- denum is controlled by gallbladder contraction and sphincter of Oddi tone. Agents that cause gallbladder contraction, including cholecystokinin, secretin, and motilin, also relax the sphincter of Oddi (Table 15.20.2). Factors modulating biliary motility have re- ceived increased attention recently with the realization that the syn- drome of biliary dysmotility may be the cause of biliary-type pain in some cases. Changes in gallbladder motility may also be important in gallstone pathogenesis. Cellular elements Hepatocytes Hepatocytes are arranged in unicellular plates (Remak's plates) that branch and divide around sinusoids, and are covered by spe- cific membranes at each surface: sinusoidal (70% of surface area) for exchange of material between the Disse space and intracellular compartment (endo- and exocytosis); canalicular membrane (15%) for exchange with the smallest of biliary canaliculi or hemicanals; and lateral membrane (15%) separated from the former by tight junctions and involved in intercellular transport between hepato- cytes. There is abundant smooth and rough endoplasmic reticulum, numerous mitochondria, glycogen stores, and an extensive cyto- skeleton. The metabolic functions of hepatocytes are discussed in 'Metabolic processes'. Hepatocytes have an immense regenerative capacity and will proliferate in the face of loss due to necrosis, apoptosis, or iat- rogenic surgical resection. If proliferative capacity is lost due to exhaustion or damage, hepatocytes may be derived from pro- genitor cells located in the canals of Hering and nearby small bile ductules. Other cell types Other cells making up 6% of all parenchyma include sinusoidal lining endothelial cells, Kupffer cells, lymphocytes, hepatic stel- late cells (Ito cells, fat-storing cells), and pit cells (intrahepatic lymphocytes) (Table 15.20.1). These cells each differ in morph- ology, patterns of function, reactions to stimuli and disease, and expression of surface molecules and receptors. Interplay between these cells is critical, with communication via tight junctions al- lowing complex modulation of hepatocyte growth and function by sinusoidal lining cells. Parenchymal cells may clear mediators, including cytokines, secreted by endothelial lining and Kupffer cells. Waves of cellular activity may pass down the length of si- nusoids. Importantly, some cells show heterogeneity of function relative to their zonal location. Periportal hepatocytes differ from

Table 15.20.1 Hepatic parenchymal cellular elements and physiological functions

Cell type	Percentage of parenchyma	Surface receptors	Cellular functions
Hepatocytes	94	Asialoglycoprotein receptors, IL-6, cytokine receptors, albumin, transferrin, mannose, annexin, MHC class 1, Fas ligand	Maintain glucose, amino acid, ammonia, and bicarbonate homeostasis. Bile

acid synthesis and transport. Synthesis of most plasma proteins. Processing of absorbed nutrient fuels and xenobiotics. Lipoprotein metabolism. Processing of hormones and signal mediators Endothelial lining cells 2.5 Scavenger receptor, Fc IgM, MHC class II (CD4), CD58, thrombospondin receptor Acts as physical barrier lining to sinusoids allowing passage of molecules via fenestrations up to 100 nm or numerous pinocytotic vesicles. Receptor-mediated uptake of HDL, LDL by scavenger receptor. May express numerous adhesion molecules marginating leucocytes and lymphocytes to sites of inflammation Kupffer cells 2 KP-1, (CD68), Fc and complement receptors, VCAM, ICAM-1 Phagocytosis of numerous particles including cellular debris, denatured albumin, bacteria, complement. After stimulation, release inflammatory mediators: oxygen radical species, nitric oxide, proteases, TNFα, IL-1, IL-6, IL-10, TGFβ, prostanoids, interferons Stellate, fat storage, or Ito cells 1.4 Retinoid, cytokine receptors, platelet-derived growth factor, TGFβ, endothelin receptor Vitamin A storage. Under a wide range of stimuli, including TNFα, TGFβ, acetaldehyde, CCL4, prostanoids, cytokines, and oxygen species, transform into myofibroblasts. Secrete extracellular matrix proteins after activation (collagen, fibronectin, laminin, chondroitin sulphate, hyaluronic acid) resulting in fibrogenesis. Activated transformed stellate cells control sinusoidal blood flow Pit cells 0.1 CD2, CD18 Natural killer cell activity that may be directed against tumour cells and virus- infected cells and occurs without prior activation Tight Endothelial cell process Kupffer cell Basolateral hepatocyte membrane with microvili junction Stellate cell Lateral membrane Endothelial lining cell Disse space Fig. 15.20.5 Hepatic sinusoid, sinusoidal cells, and functional spaces.

15.20 Structure and function of the liver, biliary tract, and pancreas 3037 perivenous cells in both the direction of carbohydrate metabolism and ammonia/glutamine synthesis. Ito cells show zonal differ- ences in desmin and cytokeratin staining, vitamin A storage, and α-smooth muscle actin. Endothelial lining cells These cells are central to the processes that control entry and exit trafficking of molecules from the sinusoidal flow into the Disse space. Fenestrae with a diameter of 100 nm, occupying up to 8% of the sinusoidal surface, act as a physical barrier to access of par- enchymal cells by large molecules including lipids, cholesterol, vitamin A, and possibly some viruses. Endothelial cells also pos- sess numerous specialized endocytotic mechanisms, some linked to specific receptors including mannose, transferrin, caeruloplasmin, modified high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucosaminoglycans, and hyaluronic acid. Nonspecific endo- cytosis of molecules and small particles up to 0.1 μm also occurs. Endothelial cells are also capable of expressing a range of surface adhesion molecules including E- and P-selectins, intercellular ad- hesion molecule 1 (ICAM-1), and lymphocyte function-associated antigen-4 (LFA-4) that enhance polymorphonuclear leucocyte and lymphocyte adherence, activation, and migration towards sites of inflammation. Kupffer cells These cells represent part of the mononuclear phagocyte system and are adherent to the sinusoidal surface of endothelial lining cells, predominantly in a periportal distribution. Covered with nu- merous microvilli and with a number of intracytoplasmic vesicles, their main function is to phagocytose a range of particulate ma- terial including cellular debris, senescent red blood cells, parasites, bacteria, endotoxin, and tumour cells. Phagocytosis is via a range of mechanisms including coated pits, macropinocytotic vesicles, and phagosomes aided by opsonization of particles by fibronectin or opsonin. Kupffer cells may be activated by molecules including Escherichia coli endotoxin, interferon-γ, tumour necrosis factor- α (TNFα), and arachidonic acid as well as zymosan and phorbol myristate to release a range of inflammatory mediators that include oxygen radical species, nitric oxide, proteases, TNFα, interleukins 1, 6, and 10 (IL-1, -6, -10), transforming growth factor-β (TGFβ), prostanoids, and

interferon-α and -γ. Some of these may act in an autocrine or paracrine loop to further activate other Kupffer cells. These inflammatory products have a range of effects including sig- nificant modulation of parenchymal cell function (downregulation of albumin synthesis and upregulation of acute-phase protein gene expression), and induction of adherence of polymorphonuclear leucocytes and lymphocytes to endothelial lining cells due to en- hanced expression of endothelial adhesion molecules. Lymphocytes Lymphocytes are present in large numbers in the normal human liver. All subsets are represented (NK, NKT, CD4+, and CD8+ cells). Some are terminally differentiated and others naïve, traf- ficking through the liver in search of antigens. In inflammatory disease processes, lymphocyte recruitment increases. The pattern of recruitment is variable and provides distinct inflammatory pat- terns. For example, portal-based inflammation in primary biliary cholangitis and primary sclerosing cholangitis, and parenchymal inflammation in autoimmune hepatitis and infection with hepa- titis viruses. Hepatic stellate cells Stellate cells (Ito cells, fat-storing cells) have a similar morphology to fibroblasts with the addition of fat droplets, and are located within the Disse space. A fine branching array of cytoplasmic processes circle sinusoids under the endothelial cells. Stellate cells contain most of the body's stores of vitamin A. Retinoids are taken up from chylo- microns by specific receptors on hepatocytes and stellate cells and stored within the latter. These cells are central to the process of hep- atic fibrogenesis, responding to mediators released by parenchymal and Kupffer cells, causing transformation into myofibroblasts. TGFβ initiates this process, stimulating production by the transformed stellate cell of extracellular matrix products (collagen types I, III, and IV, fibronectin, laminin, chondroitin sulphate, and hyaluronic acid) in addition to products for matrix degradation (collagenase, metalloproteinase, and its inhibitor TIMP-1). Activation of stellate cells is also an important mechanism for control of sinusoidal perfu- sion, through cytoskeletal actin within branching cellular processes beneath the endothelium. Pit cells Similar to large granular lymphocytes and located in clefts within endothelial lining cells, pit cells have natural killer cell properties with spontaneous activity against tumour cells in the absence of prior activation. They may also play a role in hepatic regeneration. Physiological processes Hepatic blood flow The liver receives approximately 25% of cardiac output, one-third from the hepatic artery and two-thirds from the portal vein with a plasma flow at rest of 1600 ml/min in women and 1800 ml/min in men. Hepatic blood flow increases after feeding and with expir- ation and decreases with standing, inspiration, and sleep. In con- trast to other organs, metabolic autoregulation of blood flow is not observed. Changes in hepatic oxygen consumption do not seem to control hepatic blood flow. Vascular autoregulation of hepatic Table 15.20.2 Physiological effects of neurotransmitters and hormones on biliary function Contraction Relaxation Gallbladder motility Acetylcholine Secretin Cholecystokinin Glucagon Motilin Vasoactive intestinal peptide β-Adrenergic agents Pancreatic polypeptide Endorphins Sphincter of Oddi Secretin Cholecystokinin Motilin Vasoactive intestinal peptide β-Adrenergic agents Pancreatic polypeptide

 arterial blood flow mediated by adenosine is present, but may not be of great physiological importance. Hepatic arterial resistance in- creases with increasing hepatic venous pressure due to a stepwise myogenic response in the hepatic artery to increased pressure. There is an important reciprocity between portal venous and hep- atic arterial flow with a reduction in portal venous input being asso- ciated with a significant compensatory decrease in hepatic arterial resistance and rise in arterial flow. The mechanism for this relation- ship is unproven but may be due to adenosine-mediated arterial vasodilatation. The portal venous system is passive, without pressure-dependent autoregulation, and the major physiological factors controlling flow are those modulating supply to the intestines and spleen. The

sites of portal venous resistance are not fully defined in humans but may be at sinusoidal or postsinusoidal levels. The significant capacitance of the hepatic circulation, with blood comprising up to 20% of liver volume, is reflected in the important role of the liver and splanchnic circulation in acting as a blood reservoir. Sympathetic nerve stimulation may reduce hepatic blood volume by up to 50%. Sinusoidal perfusion Blood pressure in sinusoids ranges from 4.8 to 1.7 mmHg, with flows of 270 to 410 ml/s. There is likely to be considerable hetero- geneity of the unidirectional sinusoidal flow, control for which can be considered as either passive (haemodynamic) or active. Passive control mechanisms include (1) the arterial input pressure and flow at the level of the arteriosinous twig at the origin of the sinusoid; and (2) changes in right atrial pressure, central venous pressure, and hepatic venous pressure that are transmitted to the sinusoid from the centrilobular veins. Active control mechanisms include (1) the presence of 'functional' sphincters at the inlet and outlet of the sinusoid due to indentations by the cell bodies of si- nusoidal lining cells, which under different physiological stimuli may change dimension and alter sinusoidal perfusion; (2) plug- ging by leucocytes, which are less compressible than erythrocytes and may under physiological stimuli adhere to endothelial lining cells; (3) activation of Kupffer cells within sinusoids and release of other vasoactive mediators including nitric oxide, cytokines, and prostanoids; and (4) transformation of hepatic stellate cells into activated contractile myofibroblasts that constrict the sinusoidal lumen. Sinusoidal flow will also affect the transendothelial traffic into and out of the Disse space by the processes of forced sieving and endothelial massage that may affect, respectively, the passage of lipoprotein particles and the appropriate mixing of the inter- stitial fluid. Therefore, sinusoidal flow is likely to have a profound effect on numerous hepatic metabolic functions and clearance of xenobiotics. Bile formation The formation of bile by hepatocytes and its modification by bile ductular epithelium serves many functions (Table 15.20.3). In hu- mans, the daily production of 600 ml of bile is made up of 75% of canalicular origin and 25% from ductules. Bile is formed by osmotic filtration, with the secretion of the two primary bile salt anions, taurine and glycine conjugates of cholic acid and chenodeoxycholic acid, across the canalicular membrane by an active transport mech- anism against a concentration gradient of 5000:1 (Fig. 15.20.6). Negatively charged intercellular tight junctions prevent back diffu- sion of these anions, allowing the selective passage of cations, pre- dominantly sodium, and to a smaller extent potassium, calcium, and magnesium, followed by the passive transit of water, transcellularly Table 15.20.3 Physiological functions of bile Digestion Neutralization of duodenal pH Bile salt activation of lipase, formation of micelles Emulsification, lipolysis, and solubilization of fat Absorption of fat-soluble substances Excretion, including xenobiotics Cholesterol Bilirubin Drugs Environmental toxins Heavy metals Mucosal immunity Secretory IgA Cholic acid Cholesterol Bilirubin glucuronide Organic cations Phospholipid NTCP Basolateral membrane Conjugated bile salts Glutathione Chenodeoxycholic acid OATP GSHT MDR3 MDR1 BSEP cMOAT Enterohepatic circulation Canalicular membrane Conjugated bile salts Bacterial action Ileum and colon Lithocolic acid Deoxycholic acid Fig. 15.20.6 Bile salt metabolism and enterohepatic pathway. ATP- dependent bile export—bile salt-dependent bile flow; BSEP, bile salt export pump; GSHT, glutathione transporter—glutathione transport independent of bile flow; MDR1, multidrug resistance—organic cation, xenobiotic export; MDR2, bilirubin glucuronide export—bile salt- independent bile flow; MDR3, multidrug resistance—translocation of phosphatidylcholine; NTCP, Na-taurocholate cotransporters—conjugated bile salt uptake from portal blood; OATP, organic anion transporter—bile salt, organic anion, and amphipathic solutes uptake.

15.20 Structure and function of the liver, biliary tract, and pancreas 3039 or between cells. The resulting bile salt-dependent bile flow makes up 50% of canalicular bile flow, with the remaining bile salt- independent flow resulting from the active secretion of bicarbonate and glutathione. Bile in biliary ductules is further modified by reabsorption of glucose, amino acids, and bile salts, as well as active secretion. Reabsorption of bile salts, the cholehepatic shunt pathway, occurs after their protonation in bile with the generation of further bicar- bonate into bile stimulating bile flow. Active secretion of bicarbonate and chloride within ductules is mediated by the secretin receptor and the cystic fibrosis transmembrane receptor. Gallbladder epithe- lium further modifies and concentrates bile by an active anion trans- port process. Bile salt conjugates secreted from hepatocytes into bile are deconjugated in the jejunum and ileum with reabsorption and re- uptake by the liver—this enterohepatic circulation conserves bile acids and maintains their high concentration within bile. The 5% of bile acids passing through the ileocaecal valve are fully deconjugated by colonic bacteria and reabsorbed as the secondary bile acids deoxycholic acid and lithocholic acid, which are in turn secreted as taurine and glycine conjugates. Metabolic processes Hepatic metabolic processes have a central role in protein, carbohy- drate, and lipid metabolism and fuel economy, orchestrating a di- verse interplay between central splanchnic and peripheral organs. Interruption to these processes results in the major metabolic con- sequences of acute and chronic liver disease. Modulation of these metabolic processes can occur at a number of levels. Transport of molecules across membranes and through cells is an important control mechanism as are rate-limiting enzyme levels, controlled at a number of transcriptional and translational points. There is im- portant zonal heterogeneity of hepatocyte function, with periportal zone 1 cells with a higher oxidative capacity and larger mitochondria involved in gluconeogenesis, β-oxidation of fatty acids, amino acid catabolism, ureagenesis, cholesterol synthesis, and bile secretion, whereas perivenular cells are more involved with glycolysis, lipo- genesis, ammonia clearance with glutamine synthesis, detoxifica- tion, and biotransformation. Bilirubin metabolism The first step in the production of bilirubin is the formation of biliverdin IXa by the action of haem oxidase on haem-containing proteins including catalases, cytochromes, as well as haemo- globin in senescent red cells, with the release of carbon monoxide and Fe^{2+}. Biliverdin convertase within the cytosol reduces bili- verdin to unconjugated bilirubin (Fig. 15.20.7). Both biliverdin convertase and haem oxidase are predominantly found within reticuloendothelial cells. Bilirubin is transported within plasma bound with high affinity to albumin. A few substances may displace bilirubin from albumin, including sulphonamides and fatty acids. Unbound bilirubin, which is insoluble in water, is present only in nanogram quantities but may cause significant cellular toxicity in neonates and in the Crigler–Najjar syndrome. Bilirubin uptake by hepatocytes occurs via an organic anion- binding protein receptor. Within the hepatocyte, the unbound bilirubin is transported by organelles and a number of transport proteins including glutathione-S-transferase (ligandin) to the endo- plasmic reticulum. This reduces back diffusion into sinusoids of the lipid-soluble unbound bilirubin. Glucuronidation to the mono- and diglucuronides renders bilirubin water soluble. Secretion across the canalicular membrane occurs at the canalicular multispecific membrane organic anion transporter. Bile salt metabolism In addition to their role in digestion, bile acids are the principal mechanism for clearance and metabolism of cholesterol, which acts as a substrate for their synthesis and in turn promotes biliary cholesterol secretion as lamellar vesicles. The first step in bile acid synthesis is rate limiting and involves cholesterol 7α-hydroxylase. Transcriptional control of the cholesterol 7α-hydroxylase gene has been demonstrated with thyroxine and glucocorticoids increasing, and glucagon decreasing, gene expression. Preformed (nondietary) cholesterol and bile acids may also control this enzyme. The close association between bile acid and cholesterol

metabolism is reflected in the often parallel activation of 7α-hydroxylase and HMG-CoA reductase, which is of critical importance in bile acid synthesis. The two major bile acids, cholic acid (60% of bile acid pool) and chenodeoxycholic acid, are secreted into bile as taurine and glycine conjugates. The transport receptors for both uptake into hepato- cytes and transport across the canalicular membrane are controlled at both transcriptional and post-transcriptional levels by multiple factors including bile acids, cytokines, and hormones. Nuclear re- ceptors such as the farnesoid X and liver X receptor also regulate transcription. Carbohydrate metabolism The liver has a central role in maintaining blood glucose within a narrow margin. During fasting, hepatic glucose release is contrib- uted to by both glycogenolysis (33%) and gluconeogenesis (67%) Fig. 15.20.7 Metabolism of haem and bilirubin with clearance through canalicular membrane to bile.

section 15 Gastroenterological disorders 3040 from lactate, pyruvate, glycerol, and the glucogenic amino acids alanine and glutamine (Fig. 15.20.8). This process is regulated by at least four levels: (1) hormonal control, with glucagon accounting for up to two-thirds of basal fasted glucose output, and cortisol, growth hormone, and catecholamines also contributing; (2) the supply of substrates, fatty acids, lactate, pyruvate, and amino acids for hepatic gluconeogenesis; (3) metabolic regulation of hepatic en- zyme activity; and (4) the degree of hepatocellular hydration. The direction of gluconeogenesis or glycogenolysis is controlled at the level of three paired enzyme cycles—glucose/glucose 6-phosphate, fructose 6-phosphate/fructose 1,6-bisphosphate, and pyruvate/ phosphoenolpyruvate. In contrast, after a glucose load, insulin sup- presses hepatic glucose release and activates glucose synthetase, while autoregulation of hepatic glucose extraction by glucose itself within the portal venous circulation is an important factor in con- trolling the distribution of the load between liver and peripheral tissues. Amino acid and ammonia metabolism The liver is the most important organ in controlling the plasma concentration of amino acids. During prolonged starvation, hep- atic proteolysis stimulated by glucagon increases splanchnic export of amino acids, whereas during the postprandial absorptive state, amino acid uptake is significantly increased. The gluconeogenic amino acids are preferentially extracted and metabolized, whereas the branched-chain amino acids valine, leucine, and isoleucine are only cleared in the liver for protein synthesis and are catabolized in the muscle. During sepsis and under the influence of cytokines IL-1, IL-6, and TNFα, the liver may significantly enhance gluconeogenesis and protein synthesis of acute-phase reactants (C-reactive protein, serum amyloid A). The liver has a critical role in clearing portal venous ammonia generated within the gut lumen, by both formation of carbamoyl phosphate and entry into the urea cycle in periportal hepatocytes, and glutamine synthetase-driven glutamine synthesis in perivenous hepatocytes. Protein synthesis Most circulating plasma proteins with the exception of immuno- globulins and von Willebrand factor are produced by hepatocytes. The major controlling factors for this constitutive protein secretion are substrate delivery and the degree of hydration of hepatocytes. Acute-phase protein secretion is also specifically controlled by cyto- kines with a reciprocal relationship to albumin and other carrier protein synthesis. Lipid and lipoprotein metabolism Figure 15.20.9 gives a simplified picture of lipoprotein metab- olism. Plasma lipoproteins are particles with an outer layer of cholesterol, phospholipids, and apoproteins and an inner core of cholesterol esters and triglycerides. The various lipoproteins differ in the relative proportions of these elements. Dietary-derived chylomicrons, consisting of more than 90% triglyceride, are pro- cessed within muscle and adipose tissue by lipoprotein lipase, ex- tracting free fatty acids and the remnant, enriched in cholesterol, are extracted by the liver—an exogenous lipid pathway. During carbohydrate feeding, free fatty acids formed within the liver are exported as very low-density lipoprotein (VLDL) and taken up by

muscle and adipose tissue with extraction of free fatty acids, leaving intermediate-density lipoprotein and subsequently LDL. Specific LDL receptors on hepatocytes or scavenger receptors on Kupffer cells remove LDL where cholesterol may be utilized for bile salt metabolism or excreted into bile. Peripheral LDL receptors in Glut-2 Transporter Glucose Alanine Glycogen Mitochondria Glucose 6-phosphate Fructose 6-phosphate Fructose 1,6-phosphate Phosphoenolpyruvate Glucose 1-phosphate Lactate Pyruvate Oxaloacetae Pyruvate Oxaloacetae Fig. 15.20.8 Carbohydrate metabolism and pathways for glycolysis and glycogenesis. Lipoprotein lipase Bile acids/cholesterol LDL receptor Dietary fat Intestine Oxidized LDL VLDL Free fatty acid MUSCLE and ADIPOSE TISSUE IDL Chylomicrons Remnant receptor LDL receptor Chylomicron remnants Scavenger receptor LDL Scavenger receptor HDL Lecithin; cholesterol acyltransferase (LCAT) EXTRAHEPATIC TISSUES Fig. 15.20.9 Lipoprotein metabolism.

15.20 Structure and function of the liver, biliary tract, and pancreas 3041 extrahepatic tissues also extract cholesterol. Export of cholesterol from peripheral tissues in HDL is modified in plasma by lecithin; cholesterol acyltransferase and LDL is formed for further recircu- lation. Further details can be found in Chapter 12.6. Pancreas Structure and function A retroperitoneal organ receiving arterial supply from splenic, su- perior mesenteric, and gastroduodenal arteries, the pancreas is com- posed of an exocrine portion centred on acini producing digestive enzymes draining through a ductal system into the duodenum, and the islets of Langerhans which make up 1 to 2% of the whole volume and are predominantly located along arterioles. Development and congenital anomalies The pancreas develops from ventral and dorsal buds of the primitive duodenum. With rotation around the duodenum, the two portions fuse together and the duct originating from the dorsal portion (duct of Santorini) forms the accessory duct while the main drainage of the gland is through the duct of Wirsung to the ampulla of Vater. Failure of ductal fusion, pancreas divisum, in which most of the gland drains through the duct of Santorini to the minor papilla, occurs in approximately 8% of the population, and in a small pro- portion may lead to recurrent acute pancreatitis. Annular pancreas results from pancreatic tissue remaining wrapped around the duo- denum during rotation of the ventral portion. Ectopic pancreatic tissue may occur in a submucosal location within the stomach and duodenum. Exocrine pancreas The pancreas secretes up to 2 litres of fluid per day although resting secretion rates are very low (0.3 ml/min). Acini are located in lob- ules draining into extralobular ducts. Cells lining the ducts se- crete bicarbonate, the major anion within pancreatic juice. The acinar cells are pyramidal with the nucleus and endoplasmic re- ticulum towards the base and zymogen storage granules towards the apex and draining duct. Two classes of proteolytic enzymes are secreted—the serine proteases and the exopeptidases. Serine proteases all require activation either by intestinal endopep- tidase in the case of trypsinogen or by trypsin itself in the case of chymotrypsin, elastase, and protease E. Serine protease act at various cleavage points whereas the carboxypeptidases A and B (exopeptidases) cleave C-terminal amino acids. The lipolytic en- zymes include phospholipase A2, lipase, and carboxylesterase. Other proteins found in pancreatic secretions include lysosomal proteins, ribonucleases, and amylase. Control of the secretory process involves hormones as well as sympathetic and parasympathetic nerve fibres. Secretin is the main stimulus to ductal bicarbonate secretion, whereas cholecystokinin, acetylcholine, and to a lesser extent gastrin and neurotensin stimu- late zymogen release of digestive enzymes at the apical membrane. Although often described as having cephalic, gastric, and intestinal phases to indicate the origin of the pancreatic stimulus, this dis- tinction is physiologically artificial since the phases run concur- rently. Somatostatin and glucagon inhibit pancreatic proenzyme secretion. Endocrine pancreas The islets of Langerhans represent an

endocrine organ consisting of four cell types: α cells secreting glucagon, β cells secreting insulin, δ cells secreting somatostatin, and PP cells secreting pancreatic poly- peptide. The β cells constitute 80% of islet volume and form the cen- tral core around which the others cells form a mantle. The principal physiological function of these cells is to maintain stable glucose concentration irrespective of substrate delivery. The β cells act as a sensor of glucose concentration over a wide range, with rapid equilibration of glucose levels across the cell membrane by the GLUT-2 transporter. The molecular basis for this sensor is considered to be glucokinase, the activity of which closely follows glucose levels. Enhanced glucose metabolism in- creases ATP/ADP ratios, which in turn blocks potassium ion channels, and the subsequent change in membrane potential allows an influx of calcium that promotes exocytosis of insulin- containing granules. Many other hormones, neuropeptides, and neurotransmitters also modulate glucose-dependent insulin se- cretion (Table 15.20.4). Table 15.20.4 Source and metabolic control of pancreatic endocrine function Source Stimuli for release Inhibitors of release Physiological role Insulin B cells Glucose, leucine, inosine, sulphonylureas Secondary stimuli: free fatty acids, arginine, alanine, acetylcholine, glucagon, GIP Hypoglycaemia, adrenaline, noradrenaline, somatostatin, insulin-like growth factor Increases rate of transport of glucose across cell membrane Enhances glycogen synthesis and inhibits gluconeogenesis; increases protein, triglyceride, and VLDL synthesis in hepatocytes Enhances protein and glycogen synthesis in muscle cells Enhances triglyceride deposition and inhibits lipolysis in adipocytes Glucagon A cells Glucose, catecholamines Secondary stimuli: glutamine, alanine, arginine, vasoactive intestinal peptide Insulin, somatostatin Stimulates glycogenolysis. Promotes gluconeogenesis from amino acids. Increases lipolysis in adipose tissue Somatostatin D cells Glucose, arginine, GIP, glucagon, sulphonylureas Sympathetic nerve stimulation Suppresses pancreatic exocrine release of insulin and glucagon Reduces gastric motility Inhibits growth hormone-releasing hormone Pancreatic polypeptide PP cells Protein intake, sympathetic nerve stimulation ? Probable inhibition of pancreatic acinar and ductal secretion GIP, glucose-dependent insulinotropic polypeptide.

section 15 Gastroenterological disorders 3042 FURTHER READING Balabaud C, et al. (1988). Light and transmission electron microscopy of sinusoids in human liver. In: Bioulac Sage P, Balabaud C (eds) Sinusoids in human liver; health and disease, pp. 87–110. Kupffer Cell Foundation, Rijswik. Erlinger S (1993). Intracellular events in bile acid transport by the liver. In: Tavoloni N, Berk PD (eds) Hepatic transport and bile se- cretion: physiology and pathophysiology, pp. 467–75. Raven Press, New York. Fiorucci S, Distrutti E (2019). The pharmacology of bile acids and their receptors. Handb Exp Pharmacol, doi: 10.1007/164_2019_238. Gumucio JJ (1999). Functional organisation of the liver. In: Bircher J, et al. Oxford textbook of clinical hepatology, pp. 437–46. Oxford University Press, Oxford. Kang S, Davis RA (2000). Cholesterol and hepatic lipoprotein assembly and secretion. Biochim Biophys Acta, 1529, 223–30. Knook DL, Wisse E (eds) (1982). Sinusoidal liver cells. Elsevier, Amsterdam. Lefkowitch J (2018). Anatomy and function. In: Dooley JS, et al. (eds) Sherlock’s diseases of the liver and biliary system, 13th edition, pp. 1–16. Wiley-Blackwell, Chichester. Tukey RH, Strassburg CP (2000). Human UDP-glucuronosyltransferases: metabolism, expression, and disease. Ann Rev Pharmacol Toxicol, 40, 581–616.

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