2 Morphology of the Liver

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1 Embryology of the liver

The development of the fertilized ovum during the first 18 days is defined as **blastogenesis** • After that, **embryogenesis** begins (lasting up to the 56th day): during this phase, the organs and organ systems are formed. • The period from the 56th day until birth is known as **fetogenesis**.

From the 18th day of gestation (with an embryo length of 2.5 mm) **hepatogenesis** begins with a thickening of the endoplasmic epithelium in the region of the caudal foregut. (The foregut is the future duodenum.) This endodermal area subsequently opens up into the liver groove. As from the 22nd day of gestation (with an embryo length of 3–4 mm), the groove widens into a diverticular recess with a cranial and caudal region. From the cranial part of the diverticulum, the liver is formed with the intrahepatic bile ducts. From the caudal part of the diverticulum, the gall bladder, ductus cysticus and ductus choledochus are formed.

► The *onset of hepatogenesis* is dependent on FGF1 and FGF2. Further FGFs of the 22 members of the FGF family have other functions during the later stages of hepatogenesis. In addition, bone morphogenetic protein (BMP) helps to induce liver development within the ventral endoderm. Important sources of signalling molecules are also found in heart and transverse septum mesenchyma.

Hepatoblasts (= primitive hepatocyte precursor cells) develop from the endodermal outgrowths of the cranial diverticulum and sprout into the mesenchymal tissue of the transverse septum. They form plates which are five to six liver cells thick (= *muralium multiplex*). The plates invade the transverse septum and surround preexisting spaces, from which the sinusoids subsequently develop. The hepatoblasts proliferate along these sinusoidal spaces, similar to a guide rail. (17) **Sinusoids** develop in situ. As the embryo continues to grow together with an increase in parenchymal proliferation, the endothelium-lined spaces become better defined. Finally, small vessels appear. In the sinusoidal endothelium, large intercellular gaps can be found, which allow the passage of haematopoietic cells. During the 8th–10th gestation week, hepatic haematopoiesis begins. In the course of postnatal life, the liver cell plates are reduced to a thickness of two cells (= *muralium duplex*); after the fifth year of life, the liver has a thickness of just one cell (= *muralium simplex*). From the 29th day of gestation, the formation and secretion of α_1-fetoprotein begins in the hepatoblasts (it is repressed immediately after birth).

The mesenchymal framework of the transverse septum forms the stroma, capsule and mesothelium of the liver; the mesoderm on the surface becomes its peritoneal cover. As the liver invades the transverse septum, the mesenterium is split into two membranes: the lesser omentum and the falciform ligament. As from the 6th week, the liver expands due to its rapid growth, into the abdominal cavity. At this point, the two liver lobes are already recognizable. The embryo now has a length of 10 mm.

In the 6th embryonic week, the **canaliculi** begin to develop between three to seven neighbouring parenchymal cells (the embryo is now in the 10 mm stage). Bile duct epithelia form in the vicinity of the portal vein branches; they are derived from hepatoblasts (i. e. of hepatocytogenic origin). These ductular cells are seen as a kind of cuff around the "portal" ramifications and thus create a double-layered epithelial sleeve, the so-called **ductal plate** (J.A. Hammar, 1926). • As from the 12th embryonic week, remodelling of the ductal plate into the interlobular bile ducts takes place, whereby surplus bile ducts are degraded. Bile secretion commences after the 16th week. Principally, the formation of the bile ducts is completed by the 28th embryonic week. Cholangiogenesis is accompanied by the expression of various keratin profiles, e. g. type 7, 8, 18 and 19. (8, 60)

► However, the intrahepatic bile-duct system is still immature at birth; that means the final development of the smallest ramifications takes place during the first few neonatal weeks. At this stage, the intrahepatic biliary system is most susceptible to noxae, which can lead to paucity or even atresia of the bile ducts. (s. p. 696)

The **Ito cells** appear in the 6th to 8th week of gestation. **Kupffer cells** develop as from the 3rd embryonic month; they are most probably derived from primitive macrophages built up in the yolk sac or from haematopoietic stem cells.

Already in the 6th week (= 10 mm stage), the first haematoblasts appear, and the liver begins to assume the task of **haematopoiesis**. In the 7th week (= 12 mm stage), the first blood-forming islands develop. They invade all the hepatic parenchyma, but are more pronounced in the right lobe of liver. The maximum activity of haematopoiesis is evident in the 6th and 7th month; after that, it is repressed, as the bone marrow becomes haematopoietic. At birth, the foetal liver contains only a few disseminated islands, which disappear in the first weeks of life. Lymphocytic cells are detectable as from the 14th week of gestation.

The vitelline (= omphalomesenteric) veins form a capillary plexus. Anastomotic capillaries connect the vitelline venous plexus with the umbilical veins. In the 6 mm embryo, a large venous trunk develops in the sinusoidal system and shunts blood directly from the umbilical vein to the inferior vena cava. The **duct of Arantius** persists until birth, when it atrophies; 10 to 20 days later, it leaves as a vestige the ligamentum venosum. In reality,

the ductus venosus should be called duct of Vesalius, because Vesalius recognized this anastomosis in 1561, whereas Arantius did not make his observation until 1564. (s. p. 9) The segment of the umbilical vein between the umbilicus and the liver regresses into a fibrous cord, the round ilgament (= lig. teres hepatis). The definitive vascular pattern of the liver is established around the 6th week (= 17 mm stage). The initially paired umbilical vein changes markedly; the right vein and the proximal portion of the left umbilical vein rapidly disappear. (78)

1.1 Liver stem cells

R. Virchow founded **"cellular pathology"** in 1858. He postulated that illnesses resulted from disturbances of the cells. Later, **"cellular therapy"** developed, whereby missing or malfunctioning cells are replaced by intact cells. • This is accomplished by the healthy organism itself with the help of various body cells; however, only cells of the same type can be renewed: thus they are only unipotent in terms of *"reparative medicine"*.

Stem cells are cells which reveal no or only slight differentiation; they are not yet predetermined for their later function in the growing organism. Stem cells possess two fascinating capabilities: (*1*.) they are able to multiply in an unlimited fashion and to regenerate continuously; (*2*.) they are able to produce highly differentiated progenitor cells.

Adult stem cells are detectable during an individual's whole life, e. g. in bone marrow, in the brain and liver, but also initially in the umbilical cord. Their task is to replace necrotic tissue by differentiating into cells of the same tissue (= *reparative medicine*). During the process, they may lose the ability to divide, but can also fulfil tissue-specific tasks. Since the cells only differentiate into cell types of the same tissue, they must be regarded as *multipotent*.

► In 1963, J. Till et al. detected multipotent blood stem cells in the bone marrow of mice. These stem cells were capable of forming leukocytes, erythrocytes, monocytes and thrombocytes.

Embryonic stem cells exist in two forms: (*1*.) stem cells which are only found in the *blastomere stage* up to the first segmentation: this consists of a cell cluster (= morula) with 50–150 cells in a phase 4–5 days after fertilization of the ovum. These stem cells are *totipotent* (= omnipotent), i. e. it is still possible for all of the approximately 210 cell forms in the human being to develop from these cells. (*2*.) Stem cells in the *blastocyst stage* are *pluripotent*, i. e. it is possible for all types of body cells of the three germ layers (endoderm, mesoderm, ectoderm) to develop from these cells – however, they cannot become placenta cells. If no stimuli are given for cell-specific differentiation, the embryonic stem cells will divide and each daughter cell will remain pluripotent. Due to their unique capacity to combine unlimited expansion and pluripotency, these cells must be seen as a possible source for *"regenerative medicine"* and tissue replacement in cases of injury or disease.

► In 1998, J. Thomson was the first investigator to isolate embryonic stem cells from a seven-day-old human embryo, which had been fertilized in vitro, and to use them for culturing several cell lines.

Liver stem cells: In 1958, J.W. Wilson and E.H. Leduc postulated the presence of liver stem cells (LSC) for the first time. They are considered to be genuine and participate in the normal turnover of the liver parenchyma. Such LSCs (7–15 μm) have multilineage differentiation potential and self-renewal capability, similar to the cells of the cranial and caudal diverticulum after the 6th week of gestation. • In addition, so-called **oval cells** can be found. They are formed from terminal periductular cells. The population comprises immature small cells with a scant cytoplasm and ovoid nuclei. Such cells can differentiate into hepatocytes and biliary epithelial cells. In the case of severe liver injury, the regenerative potential of the stem cells and/or oval cells is activated. In the adult liver, both LSC and oval cells are able to replace parenchymal loss. Apparently, specific signalling substances are required for stimulating the regeneration mechanism. An important stem cell growth factor is G-CSF (= granulocyte-colony stimulating factor). • A **third population** of stem cells with hepatic potential is found in the bone marrow. It was possible to transform these stem cells into hepatocytes. However, it remains unclear in what way these three stem cell populations work together to replace parenchyma. (14, 51, 56, 79)

There are three different mechanisms for **regeneration** of the liver: (*1*.) transdifferentiation of LSCs into hepatocytes and biliary epithelial cells, (*2*.) proliferation of oval cells as so-called liver progenitor cells, and (*3*.) division of hepatocytes. The last mentioned process is of less importance with regard to regeneration following resection, but more so concerning loss of function of the liver parenchyma.

► Each hepatocyte can divide at least 30 times. After 60% resection, the liver regenerates without any problem within 1–2 weeks in the animal model. Such 60% resections can be repeated several times after a corresponding ten-day regeneration period. The normal turnover in terms of continued proliferation of hepatocytes and biliary epithelial cells begins in the portal zone and "streams" towards the central veins (77). In the case of severe injury of the liver, including loss of parenchyma, this process is enhanced in a carefully steered manner.

2 General anatomy of the liver

The liver is the largest solid organ in the body. • The **weight** of a normal liver comprises about 1/18 of the newborn child's body weight (approx. 5%) and about 1/50 of the adult's body weight (2.3–3%), varying in men from 1,500–1,800 g and in women from 1,300–1,500 g. The relatively larger weight in infancy is mainly due to an enlargement of the left lobe. The weight of the liver relative to body weight decreases from 3% to 2% with age. With regard to **size,** the liver is on average 25–30 cm in width, 12–20 cm in length

and 6–10 cm in thickness. The **surface** is smooth and shiny. The **colour** of the liver is brownish red. The lobular structure can be seen distinctly upon close inspection. The **position** is intraperitoneal (with the exception of the area nuda and the gall-bladder bed). (s. fig. 2.1) Due to the suction of the lung, the position of the liver depends on the position of the diaphragm; the respiratory displacement of the liver is approx. 3 cm. (s. fig. 4.3)

2.1 Topography

The topography of the liver is characterized by the (smaller) *left lobe* and the (about six times larger) *right lobe*, which are separated by the (translucent) *falciform ligament*. This peritoneal duplicature splits dorsad into a right and left coronary ligament of liver; both terminate in the left and right triangular ligament; the right part finally ends as the hepatorenal ligament. (s. figs. 2.1, 2,5; 16.4)

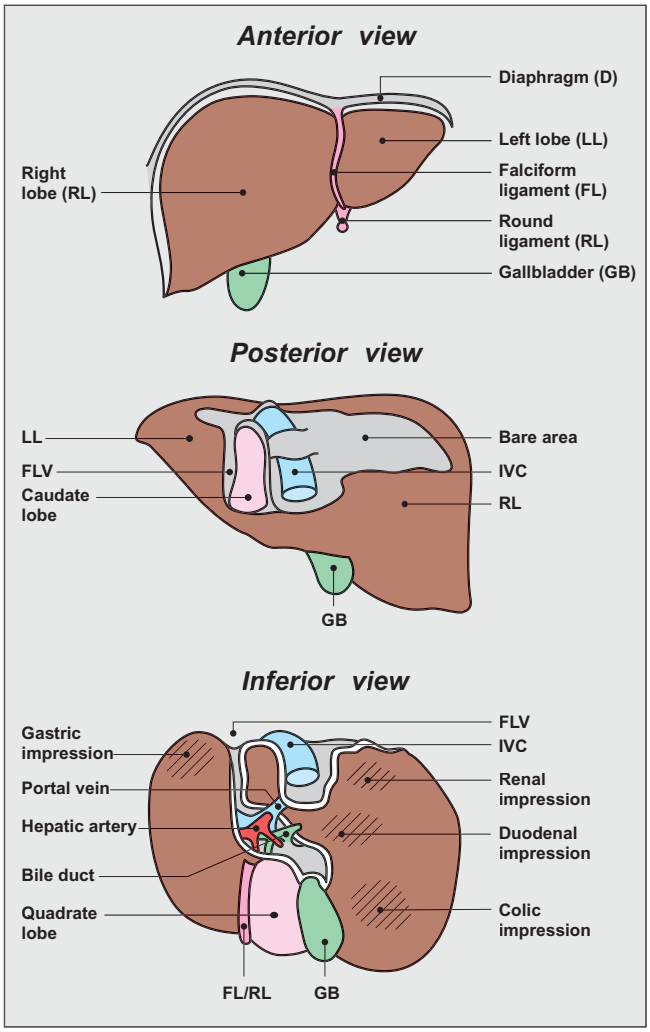

Fig. 2.1: Views of the liver: anterior, posterior, inferior. (LL = left lobe, RL = right lobe, D = diaphragm, GB = gall bladder, FLV = fissure for ligamentum venosum, RL = round ligament (= lig. teres), IVC = inferior vena cava, FL = falciform ligament)

The *round ligament* (= lig. teres) is a remnant of the umbilical vein of the foetus. It runs in the free edge of the falciform ligament (during the time of foetal development, it actually joins the left branch of the portal vein) and is often coated by drop-shaped mesenteric fat tissue. The *ligamentum venosum* is a slender remnant of the duct of Arantii in the foetus. (s. p. 9!) • On the inferior liver surface – separated by the portal vein – are the *quadrate lobe* (lying anteriorly between the gall bladder and round ligament) and the *caudate lobe* with papillary tubercle and caudate process (lying posteriorly along the inferior vena cava in front of the hepatic porta). This *hilum of the liver* in the centre of the inferior liver surface consists of the proper hepatic artery, portal vein, common hepatic duct, lymph vessels, and hepatic nerve plexus. These are held together by the perivascular fibrous capsule. (s. fig. 2.1)

With its convex **diaphragmatic surface,** the liver, which faces forwards and upwards, abuts the arch of the diaphragm and the anterior abdominal wall. It bears a flat cardiac impression. This diaphragmatic surface is differentiated into the *pars libera* (covered with peritoneum) and the *pars affixa* (= area nuda). • The **visceral surface** inclines both backwards and downwards. The superior and inferior surfaces form together the sharp liver margin (*margo inferior*). The inferior surface may show impressions caused by adjacent organs (gaster, colon, kidney, duodenum, gall bladder) and the posterior surface shows a *fissure* for the ligamentum venosum. (s. fig. 2.1)

2.2 Form and variants

The **shape** of the liver resembles largely that of a pyramid lying at a slant with its base towards the right side of the body. The exterior form can vary greatly. (s. p. 2)

Variations in form: In the first instance, *genetic factors* are responsible for variations. Additional *internal causative factors* worthy of mention include changes due to portal vein thrombosis, haemocongestion, cardiac cirrhosis, thesaurismosis, fibrosis and atrophy. *External causative factors* include impression effects caused by pillar of diaphragm, costal arch, xiphoid process and wearing tight belts or laced corsets. (37) • Chronic coughing may lead to mostly parallel *cough furrows* on the convexity of the right lobe, – one to six in number. (33) • *Zahn's furrows* can appear on the right surface of the liver; they generally run sagittally and are caused by hypertrophic columns as a result of chronic lung emphysema and also (more rarely) congenital factors. (s. fig. 2.2) • The posterior surface of the liver occasionally has furrows, known as *rima coeci Halleri*. A branch of the portal vein always extends beneath their bed (J. Hyrtl, 1873). • A tongue-shaped projection of the right (or more rarely the left) lobe of liver adjacent to the gall bladder is known as *Riedel's lobe* (I. Riedel, 1888). This condition may be congenital or arise due to the traction of a gall bladder enlarged by stones. Ried-

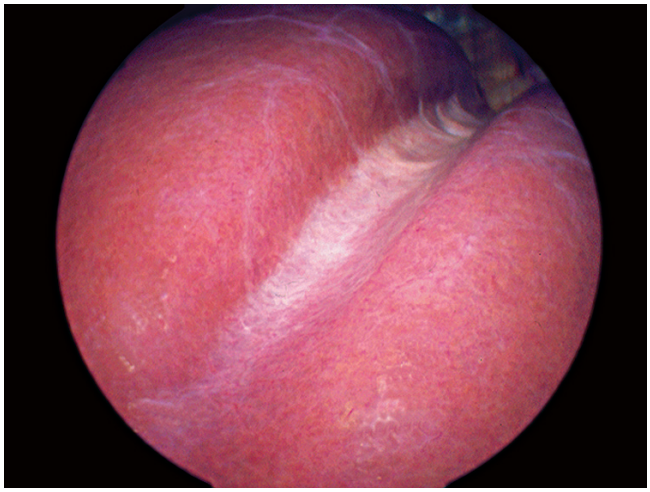

Fig. 2.2: Zahn's furrow: diagonal craniocaudal impression of a hypertrophic diaphragm contour. Along the bottom of the furrow, there is a capsular fibrosis

el's lobe is more frequent in women. It is not deemed to be a true accessory lobe. It is easily mistaken for other tumours in this area. • *Fissures* (also called "simian cleft") (s. figs. 2.3; 31,22; 35.5) − which may give rise to a hepar succenturiatum (= accessory lobe) (13) or hepar lobatum − are without clinical significance.

Variations in position: An interposition of intestinal loops (generally transverse colon) between liver and diaphragm is termed *Chilaiditi syndrome*. It is the result of hepatoptosis. • Any noticeable *relaxation of diaphragm* due to congenital muscular aplasia in the region of the right diaphragm leads to displacement of the right liver lobe into the right thoracic space. (68)

Accessory lobe: This anatomical abnormality is rare and without clinical significance. Torsions are rare findings. Up to 16 accessory lobes have been reported in a single patient. They are usually located on the inferior surface of the liver. (s. fig. 2.4) Therefore they are generally detected only during the course of imaging examinations, surgery or autopsy. In case of suspicion, diagnostic laparoscopy is indicated. Often an accessory lobe may contain its own blood, bile and lymph vessels. (13, 30, 38)

Lobar atrophy: Atrophy may develop as a result of disturbances in the portal blood supply or biliary drainage of a lobe. It is generally possible to differentiate between the two aetiologies with the help of scintigraphic methods. • Likewise, lobar atrophy (the left liver lobe is most frequently affected) may develop following necrosing processes of the parenchyma, such as those caused by acute virus hepatitis (s. figs. 21.13; 22.16), intoxications and chemoembolization, or in cases of severe inanition as well as in marked cirrhosis (s. figs. 35.1, 35.17). Compensatory hypertrophy of the opposite lobe is usually in evidence. (20, 21, 76)

Lobar agenesis: In most cases, agenesis affects the right lobe. This very rare abnormality is mostly associated

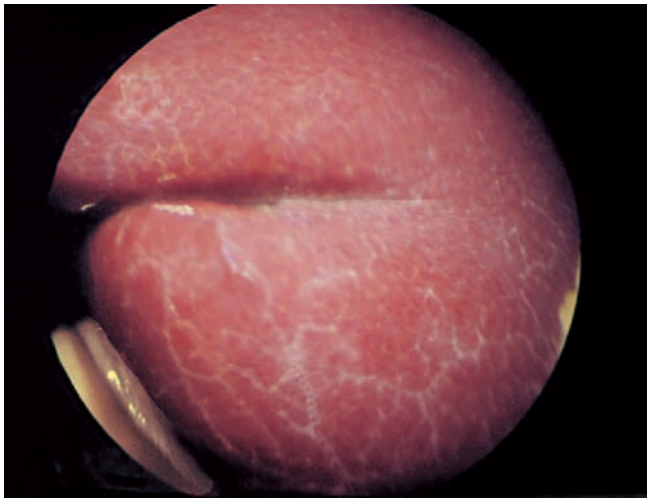

Fig. 2.3: Reticular fibrosis of the liver surface in chronic persistent hepatitis B with a so-called "simian cleft" (s. figs. 31.22; 35.5)

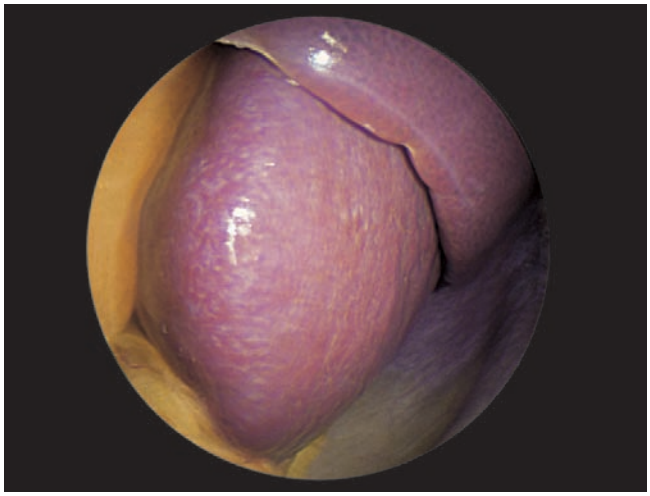

Fig. 2.4: Accessory lobe on the inferior surface of the right lobe of liver. Here shown in chronic hepatitis B

with other congenital malformations, especially of the biliary system. The unaffected liver lobe will generally develop compensatory hypertrophy. (25, 39, 47)

2.3 Segmental subdivisions

The boundaries regarding physiological topography are marked by the distribution pattern of the portal vein, the hepatic artery and the bile ducts, or according to the origin of the three large hepatic veins. The result is a clear and precise subdivision of the liver in the sense of a functional lobulation into 12 segments (3 main segments, each with 4 subsegments) or 9 segments, respectively. The essential findings are based on the investigations of C.H. Hjortsjö (1948, 1951), C. Couinaud (1954, 1957), S.C. Gupta et al. (1977, 1981), H. Bismuth (1982), and A. Priesching (1986). (s. figs. 2.5; 40.4)

Rex-Cantlie's line (H. Rex, 1889; J. Cantlie, 1898), running from inferior vena cava to gall bladder, forms the

boundary between the two portal distribution areas and thus between the right lobe (right portal vein) and the left lobe (left portal vein) of liver (= *double-flow principle of the portal vein*). Additionally, however, the left part of the right lobe of liver (segment II 1−4, so-called *"centre of the liver"*) is supplied by both branches of the portal vein. Consequently, segment II 3 (equivalent to segment IV) would correspond to the quadrate lobe, segment II 2 to the caudate process, and segment II 1,2 (or I) to the caudate lobe. The caudate lobe, which is situated in the posterior medical part of the right lobe, is also termed segment I. It contains portal venous blood from the right and left portal vein; the venous blood runs off directly into the retrohepatic inferior vena cava, and not into the hepatic veins. (s. figs. 2.5; 40.4)

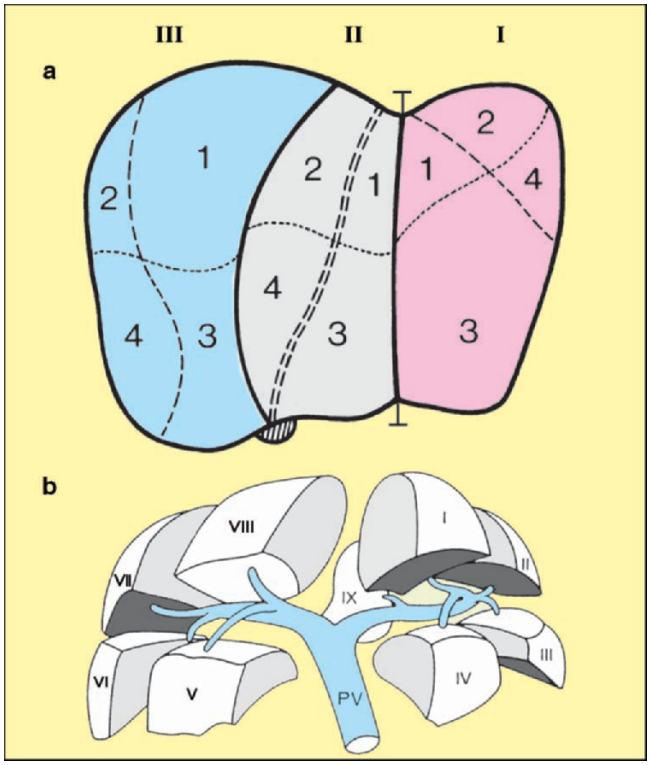

Fig. 2.5: Segmentation of the liver. • **a:** *Left lobe* (I, 1−4): 4 segments; "centre of the liver" (II): quadrate lobe (II, 3): caudate lobe (II, 1,2) and caudate process (II, 2); *right lobe* (III, 1−4): 4 segments. • Rex-Cantlie's line (= = =) as functional division between both liver lobes runs between II 2,4 and II 1,3. Topographically, the liver lobes are separated by the falciform ligament (⊢——⊣) between I 1,3 and II 1,3. • **b:** The liver can be divided into 9 segments (I−IX) according to the ramifications of the portal veins. Segments II/III, I/IV, V/VIII and VI/VII are also combined into double segments

The "portal segments" and the "hepatovenous segments" are, however, subject to considerable individual variations with respect to their size and the position of their boundaries. This point must always be considered in cases of hepatectomy. For this reason there is, as yet, no general agreement concerning the designation of the segments. (19, 67)

3 Structure and histology of the liver

In terms of structure and histology, it is possible to divide the liver into **four tissue systems:** (*1.*) intrahepatic vascular system, (*2.*) stroma, (*3.*) sinusoidal cells, and (*4.*) hepatocytes.

3.1 Intrahepatic vascular system

3.1.1 Hepatic artery

The **common hepatic artery** is a branch of the coeliac trunc (= *Haller's tripod*), from which the splenic artery, the phrenic artery and the left gastric artery emerge. In about 18% of cases there is a second hepatic artery leading out of the left gastric artery and in about 10% of cases there is a second hepatic artery leading out of the superior mesenteric artery. The common hepatic artery extends into the proper hepatic artery. Prior to this point, the gastroduodenal artery and the right gastric artery branch off. The course and the ramification of the hepatic artery are "normal" only in about 55% of cases! (57) These frequent vessel abnormalities are of great importance in surgery. • The pressure in the hepatic artery amounts to 100 mm Hg, with a pressure-dependent autoregulation of the blood flow (increase of pressure = decrease of blood flow, and vice versa).

In the hepatic porta, the **proper hepatic artery** divides into the *right branch* (from which the cystic artery emerges) and the *left branch* (from which a "middle hepatic artery" occasionally emerges). The branches of the hepatic artery run close to the portal veins and may even (rarely) coil round them in places. An arterial sphincter is located prior to the further division of the hepatic artery into smaller branches. • There are anastomoses between the arterial branches and the hepatic vein. By way of an arteriolar sphincter (45), the *interlobular arteries* branch into *intralobular arterioles*, supplying the lobules of the liver with arterial blood. The arterial blood enters the sinusoids either through terminal branches or through arterioportal anastomoses and mixes with the portal blood. The pressure in the hepatic arterioles is 30−40 mm Hg. (36, 45, 57)

The blood of the hepatic artery supplies **five regions** of the liver: (*1.*) peribiliary vascular plexus as the greatest arteriolar compartment, (*2.*) interstitium of the portal fields, (*3.*) vasa vasorum of the portal vein, (*4.*) vasa vasorum of the hepatic vein, and (*5.*) liver capsule.

► **Hepatic blood flow** amounts to ca. 1,200 ml/min in women and ca. 1,800 ml/min in men, depending on the prevailing physiological conditions. Of this blood, 70−75% are supplied by the portal vein and 20−25% by the hepatic vein. The oxygen supply is secured by the hepatic artery at 20 vol. % and the portal vein at 16−17 vol. %. • The **blood content** is equivalent to 25−30%

of liver weight. The liver blood volume accounts for 10−15% of the total blood content of the body − an extremely high proportion.

► **Oxygen consumption** of the liver amounts to 6 ml/minute/100 g wet weight. The acino-peripheral region (zone 1) has the best supply of oxygen (mainly aerobic metabolism), whereas the centroacinar region (zone 3) has the most oxygen-deficient blood (mainly anaerobic metabolism). A decrease in liver blood supply generally occurs whilst standing, during sleep, when fasting, and in old age. Oxygen extraction in the liver amounts to approx. 40%; any additional requirement of oxygen is (initially) met by a considerable increase in oxygen extraction of up to 95%. The regulation of the blood flow in the sinusoids is influenced in different ways: (*1.*) neural factors (adrenergic and dopaminergic receptors), (*2.*) anatomical mechanisms, and (*3.*) vasoactive substances (e.g. endothelin, CO, NO, adenosine).

3.1.2 Portal vein

The portal vein is formed posterior to the pancreatic isthmus by coalescence of the superior mesenteric vein and splenic vein. The inferior mesenteric vein enters at a point not far from this junction. The portal vein then runs through the hepatoduodenal ligament and absorbs venous blood from the ventricular coronary vein. • At the porta hepatis, the portal vein divides into the *right branch* (which takes in the cystic vein as well as one or two veins from the caudate lobe) and the *left branch*, into which flow the paraumbilical veins, extending through the round ligament, and the ventroflexal ramus, emerging from the left sagittal fossa. (s. fig. 2.6) • The branches of the portal vein extend (by further branching and reduction in the lumen) into the portal tracts. Here they merge with the *interlobular veins*, which generally divide into two *conductor veins* (= venulae interlobulares). The conductor veins divide into *distributor veins* and continue as Y-shaped *terminal branches* (= venulae afferentes). The portal blood passes through the periportal limiting plate of hepatocytes, entering the **sinusoids** through venous inlets. This means that the blood of the portal vein flows only into the sinusoids. Terminal branches of the arteries join up with the sinusoids separately. The outflow of sinusoidal mixed blood (75% from the portal vein, 25% from the hepatic artery) occurs via venous capillaries in the *central hepatic vein* (or *terminal hepatic vein*). The venous blood from the capillaries of the portal tract flows off either through the distributor veins or directly into the sinusoids. The difference in pressure between portal veins and hepatic veins is more important for the sinusoidal supply of blood than are the respective absolute values. (36) • These radicular portal veins, which originate in the portal fields, have therefore also been described as the *"inner root of the portal veins"* (H. Elias et al., 1949).

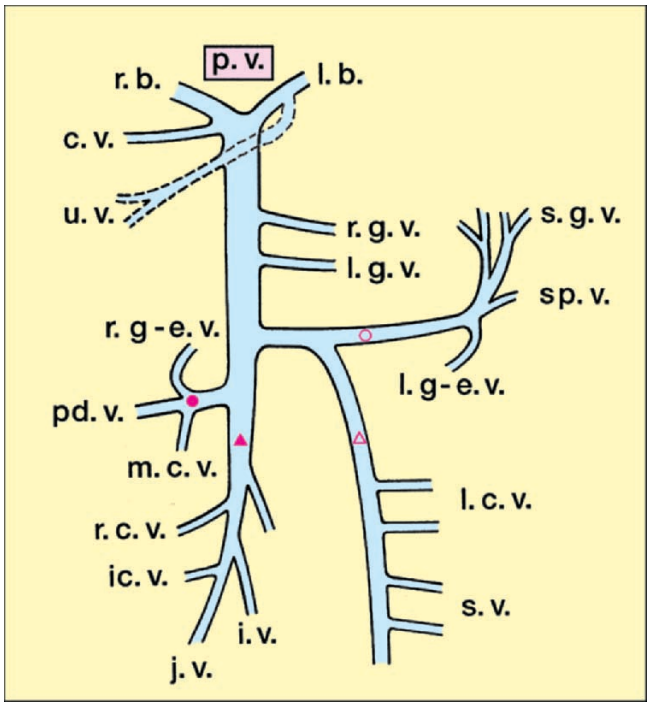

Fig. 2.6: Diagram of the portal vein: p.v. = portal vein, r.b. = right branch, l.b. = left branch; c.v. = cystic vein; u.v. = umbilical vein; r.g.v. = right gastric vein, l.g.v. = left gastric vein; sp.v. ○ = splenic vein, s.g.v. = short gastric veins, l.g-e. v. = left gastro-epiploic vein; ● = gastrocolic trunc; r.g-e.v. = right gastro-epiploic vein, pd.v. = pancreaticoduodenal vein, m.c.v. = middle colic vein; ▲ = superior mesenteric vein, r.c.v. = right colic vein, ic.v. = ileocolic vein, j.v. = jejunal veins, i.v. = ileal veins; △ = inferior mesenteric vein, l.c.v. = left colic vein, s.v. = sigmoid veins

3.1.3 Hepatic vein

The hepatic vein emerges from the *central hepatic vein* in the centre of the lobule. It runs at an acute angle into the *sublobular vein*. From the confluence of the sublobular veins, *collecting veins* are formed which fuse to form five *trunk veins*: the right and left superior hepatic vein as well as the right, left and intermediate hepatic vein (the latter two forming a common trunk in 60−70% of cases). The hepatic veins progress intersegmentally; they receive branches from adjacent segments. This group of superior hepatic veins drains into the *inferior vena cava* at the posterior surface of the liver below the diaphragm. • By contrast, the group of inferior hepatic veins (= accessory hepatic veins) is very varied in terms of number, diameter and draining sites.

3.1.4 Biliary system

The *bile canaliculus* is formed as a bile capillary by means of a groove-like canal in the intercellular space, bounded by 2 adjacent liver cells. The bile canaliculi have no walls of their own, but are surrounded by a special zone of the cell membrane (so-called *pericanalicular ectoplasm*). Their diameter amounts to 0.5−1.0 µm. They are interconnected and form an extensive polygonal network. The surface area of the bile capillaries is increased by *microvilli*,

which show great functionally determined variability. The canalicular membrane constitutes 10% of the total plasma membrane in the hepatocytes. Similar to the pericanalicular ectoplasm, the hepatocytes contain contractile microfilaments and other components of the cytoskeleton. These canaliculi are supplied with carrier proteins and enzymes to control bile secretion. (2, 34)

The canaliculi continue into an ampulla-like extension known as *Hering's canal* (E. Hering, 1866). This area can be regarded equally as the end point of the canaliculi and the beginning of the ductules, hence the term *intermediate ductule* is used (M. Clara, 1930). From here the bile ducts have their own wall of cuboidal epithelial cells. They are 7−20 µm in diameter. Their designation as *preductules* has been generally adopted. (54) Because of their extreme proneness to damage, the preductules are described as the "Achilles' heel of the liver" (L. Aschoff, 1932).

The preductules merge either with the *cholangioles* (M. Clara, 1934) or the *biliferous ductules* (H. Elias, 1949) or the perilobular ductules, respectively. Morphologically, it is generally not possible to distinguish between preductules and ductules. Thus both structures are subsumed under the term "cholangioles" or "terminal bile ducts". The ductules are followed by the *interlobular bile ducts* with a diameter of >50 µm. They run through the connective tissue wedges of the portal tracts (= Glisson's triangles). These interlobular bile ducts (15−100 µm) anastomose with each other. The larger septal (100−400 µm) and segmental (0.4−0.8 mm increasing to 1.0−1.5 mm) bile ducts continue into the *right* and *left hepatic duct*, which unite at the hepatic porta to form the *common hepatic duct*. The latter confluences directly afterwards with the cystic duct, thus forming the *common bile duct* (= ductus choledochus). (34, 49, 75)

3.1.5 Lymph vessels

The liver forms more *lymph* than any other organ of the body (0.4−0.6 mg/kg BW/min). Lymph capillaries take up lymph from **Disse's space** (J. Disse, 1890) and thereafter from **Mall's space** (F.P. Mall, 1906), which lies between the limiting plate and the portal connective tissue. Disse's space is also considered to be the main source of lymph. In addition, lymph capillaries commence in the adventitia of sublobular veins and run close to the hepatic veins as far as the paracaval lymph nodes. Lymph vessels possess valves which permit the lymph to flow only in one direction. Lymphatic vessels are present in all portal fields. They are found exclusively in the perivascular connective tissue and in the capsule of the liver. (s. fig. 16.4) • Drainage is effected by the *hepatic lymph nodes* in the area of the porta hepatis. Lymph reaches the *thoracic duct* via large valved lymphatic trunks and interconnected lymph nodes. Thus it enters the systemic circulation. (22, 64)

3.2 Stroma of the liver

The term **stroma** comprises the interstitial connective tissue of an organ. • In the liver, **four types of tissue structure** are differentiated: (*1*.) capsule of the liver, (*2*.) perivascular connective tissue, (*3*.) Glisson's portal tract, and (*4*.) reticular network.

► This **extracellular matrix** (ECM) is a dynamic concentration of complex macromolecules. (66) Besides mechanical functions, the components of ECM also have important physiological tasks; therefore they have bidirectional contacts with the liver cells. These *matrix components* include: collagens, elastin, glycosaminoglycanes, proteoglycanes, and glycoproteins. • In the liver, there are mainly **collagens** I, III (= large fibrils), IV (= net structure), and V, VI (= small fibrils). The non-fibrillar collagen type XVIII is found in the perisinusoidal space and in the basal membranes. The Ito cells are deemed the main producers of ECM. The biosynthesis of collagen comprises the intermediate steps of pre- and procollagen. The half-life of liver collagen amounts to approx. 30 days. The *degradation of collagen* occurs through matrix-metalloproteinases, which are mainly formed in the Ito cells. During the degradation process, hydroxyproline develops, which in turn is either oxidized in the liver into CO_2 and H_2O (ca. 75%) or excreted in the urine (ca. 25%). Thus the *excretion rate of hydroxyproline* in the urine is an indicator for collagen metabolism. • **Elastin** gives the hepatic structures their elasticity. Connective tissue cells secrete the precursor proelastin, which is converted into elastin; the latter then combines with collagen and glycoproteins to form elastic fibres. Degradation takes place with the help of elastase and metalloproteinases. α_1-antitrypsin is a specific inhibitor of elastase. • **Proteoglycanes** are the main component of ECM. They consist of a central protein strand with long, unbranched carbohydrate side chains (= glycosaminoglycan). This group also contains hyaluronic acid. Proteoglycans are hydrophylic and can bind cations. They are mainly built up from Ito cells and broken down by lysosomal hydrolases. • **Adhesive glycoproteins** (= *nectins*) ensure contact between ECM, hepatocytes and non-parenchymal cells. They comprise fibronectin, laminin, nidogen, tenascin and indulin. • The numerous heterogeneous components of the ECM are closely interwoven and communicate bidirectionally with the liver cells by means of special substances, so-called *integrins.*

3.2.1 Capsule of the liver

The capsule of the liver (A. von Haller, 1764) is 43−76 µm thick. It consists of the endothelial coating (= serosa) and a network of collagenous and elastic fibres. The capsule and the falciform ligament contain sensitive phrenicoabdominal branches of the phrenic nerve, which vary in extent (algesia or shoulder pain may thus accompany liver biopsy). Moreover, blood and lymph

vessels as well as rudimentary bile ducts (which may become enlarged in the case of portal hypertension, ascites or cholestasis) are present in the capsule. The small blood vessels of the capsule anastomose with branches of the portal vein, yet not with the hepatic veins. The inner surface of the capsule is intimately connected to the liver parenchyma, particularly in the area of the interlobular connective tissue.

3.2.2 Perivascular connective tissue

The perivascular fibrous capsule (F. Glisson, 1654) commences in the hepatic porta as a tree-like branching framework of connective tissue surrounding the interlobular vessels. It also surrounds the central hepatic vein and its small tributaries, which are joined to the parenchyma by radial fibres as well as being established in the portal tracts. This prevents a suction-induced collapse of the venous vessels as a result of respiration-dependent negative pressure in the pleural cavity. The perivascular connective tissue, known as *Glisson's capsule*, extends fine secondary trabeculae into the parenchyma. They contain the intralobular biliary, lymphatic and blood capillaries.

3.2.3 Lattice fibre network

The reticular network consists mainly of *lattice fibres* (O. Oppel, 1891) which lie on the hepatic cell plates and serve as a mechanical support for the sinusoids and also as a directrix in hepatocyte regeneration. The microvilli of the hepatic cells extend through this lattice fibre network into **Disse's space** (J. Disse, 1890). In general, this space is not visible in vivo, and thus the sinusoid wall appears to abut directly onto the hepatocytes. However, it constitutes about one third of the entire extracellular space in the liver, which itself accounts for 15–20% of the liver volume and 2–4% of the liver parenchyma. It is via Disse's space that the exchange of different substances between liver and blood takes place. The width of Disse's space varies between 0.2–1.0 µm, depending upon the resorptive and secretory capacity of the hepatocytes. Fluid, protein and particles up to 100 nm may, however, enter this perisinusoidal space (increasingly in hypoxia) and be drained off. The space itself lies between the trabeculae and the sinusoids. It is thought to be connected to Mall's space, but no direct connection from Mall's space into the lymph vessels within the periportal region has so far been demonstrated. (s. figs. 2.7–2.9)

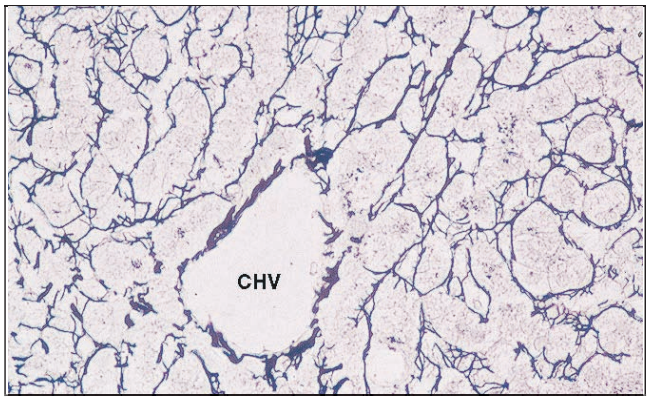

Fig. 2.7: Reticular fibre network with central hepatic vein (CHV) (Gomori's reticulin stain)

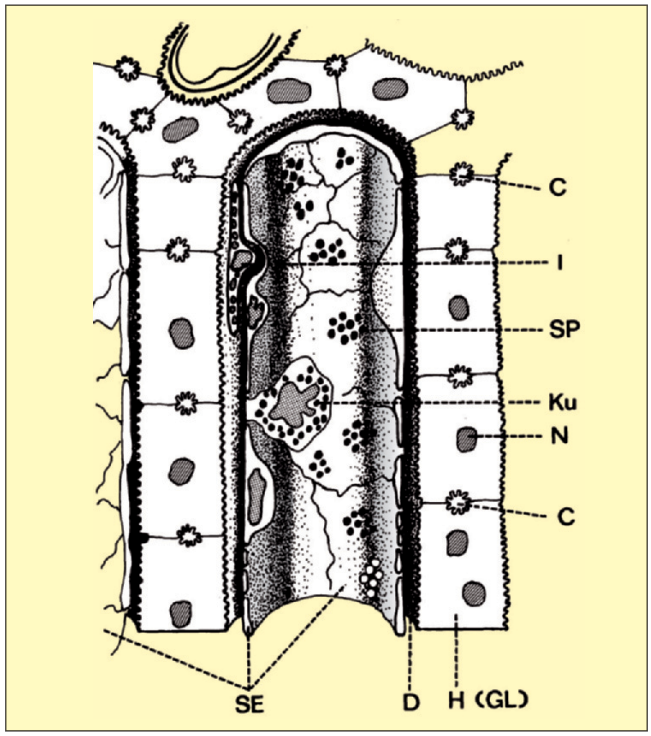

Fig. 2.8: Spatial relationship of sinusoid and hepatic cells: hepatocytes (H) in the form of boundary lamella (BL), cell nucleus (CN), canaliculus (BC), Disse's space (D), endothelial cells (E), sieve plate (SP), Kupffer cell (K), Ito cell (I). The cellular interchange area is increased by microvilli (modified from D. Sasse, 1986)

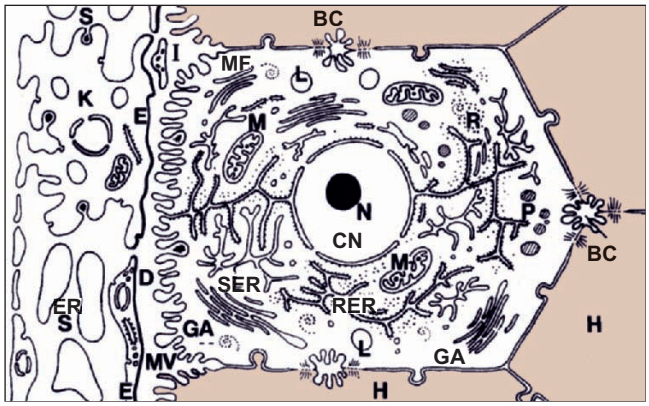

Fig. 2.9: Liver cell and sinusoidal cells with organelles and polarized membrane compartments: hepatocytes (H), sinusoids (S), Disse's space (D), erythrocytes (ER), endothelial cells (E), Kupffer cells (K), Ito cells (I), microvilli (MV), canaliculus (BC), nucleolus (N), tight junctions (tj), cell nucleus (CN), mitochondria (M), smooth endoplasmic reticulum (SER), rough endoplasmic reticulum (RER), Golgi apparatus (GA), lysosomes (L), peroxisomes (P), ribosomes (R), microfilaments (MF) (modified from L. Cossel) (s. figs. 2.16–2.18)

3.2.4 Portal tract

In the *portal tract* (= Glisson's triangle, portal field) (F. Glisson, 1659), the perivascular connective tissue with its enclosed (and protected) radicles of the portal veins, the hepatic arterioles, bile ducts, lymph vessels and nerve fibres terminates in the connective tissue covering of the perivascular fibrous capsule. Any lymphocytic infiltrations as well as occasional isolated histiocytic or monocytic forms which are embedded in this area are considered to be physiological. The continuous line of hepatocytes immediately bordering the portal tract is designated *limiting plate*. (s. figs. 2.8, 2.10, 2.12)

3.3 Sinusoidal cells

Four different *mesenchymal cell types* are subsumed under the term **sinusoidal cells:** (*1*.) endothelial cells, (*2*.) Kupffer cells, (*3*.) Ito cells, and (*4*.) PIT cells.

Although the sinusoidal cells (31 million/mg liver) make up only a relatively small proportion of the liver volume (6.3%), they constitute 30−40% of the total cell number. The total surface area of their plasma membranes is 26.5% of the total membrane surface of all liver cells. (3, 5, 29, 43, 53, 55, 59) (s. figs. 2.8, 2.9)

3.3.1 Endothelial cells

Endothelial cells constitute the greatest proportion (70%) of the sinusoidal cells. These are flat cells, the nuclei of which camber the cell body. With their slim nuclear branches, they are in loose connection with both the neighbouring endothelial cells and the microvilli of the hepatocytes. They are located on a fine layer of extracellular matrix. Their proportion of the total cell number is 15−20%, but they make up only 2.8% of the liver volume. They form a continuous lining of the **sinusoids** which, however, possesses numerous intercellular spaces (0.1−0.5 µm) (S. Minot, 1892). The sinusoids (with a total surface area of 400 m^2) are 4−15 µm wide and 350−500 µm long. Here portal blood combines with arterial blood. The entry and exit of blood is controlled by sinusoidal sphincters. (36, 73) Compared to the capillaries of other organs, sinusoids show fundamental structural differences. They are interspersed with **pores** which have a basic diameter of 0.1 µm, actively variable in width. When grouped together, such pores are known as *sieve plate*. (s. fig. 2.8) There are also larger pores (0.5 µm), so-called *fenestrae*. The smaller pores, the fenestrae and the intercellular spaces are essential for the process of filtering the components of the blood; they have scavenger functions (52) and regulate the exchange of fluid and material between the blood in the sinusoids and the hepatocytes. In addition, they are of great importance for the balance of lipids, cholesterol, and vitamin A. Endothelial cells also form and secrete cytokines (e. g. II 1, 6, IF, α-TNF), matrix components (e. g. collagens, fibronectin) and growth factors (e. g. HGF, IGF, FGF) as well as vasoactive substances (e. g. NO, endothelin). • The cells themselves can be damaged or even completely destroyed by the effect of toxins, alcohol, hypoxia, viruses or increased pressure in the sinusoids. In this case, the hepatocytes are completely "naked" and exposed to all attacks. The endothelial cells are stabilized by a network of lattice fibres. • Because of their structural and functional characteristics, the endothelial cells, Disse's space and the so-called vascular hepatocyte pole are subsumed under the term *"perisinusoidal functional unit"*. (44)

3.3.2 Kupffer cells

The stellate cells initially determined by K. W. von Kupffer (1876) by means of the gold chloride method were actually Ito cells located in Disse's space. It was not until 1898 and 1899 that the sinus macrophages were described by von Kupffer again − though at this point not sufficiently differentiated from the gold-reactive fat-storing cells.

Kupffer cells constitute about 25% of the sinusoidal cells. They make up 8−12% of the total liver cells and 2.1% of the liver volume. Their overall number/mg of liver amounts to 31,000, the half-life being 12.4 days. They probably derive from monocytes and are released by stem cells in the bone marrow. Thus they belong to the mononuclear phagocytosis system (MPS) (R. van Furth et al., 1970). Kupffer cells can multiply by mitosis. Their villiform surface (fuzzy coat) and irregular, mostly star-shaped form led to the designation "stellate cells". They are randomly distributed in the sinusendothelium, but occur three to four times more frequently in the periportal region than in the perivenous zone. They connect with adjacent cells or spaces by means of ramifications and through pores. Their cytoplasm contains numerous organelles. Charged Kupffer cells may be flushed out with sinusoidal blood. • *Phagocytosis* can be seen as the most important function of Kupffer cells. Apart from the cells at the base of the pulmonary vascular bed, they have the greatest intravascular phagocytic capacity. Further functions include (*1*.) *pinocytosis*, (*2*.) discharge of *signal substances* (e.g. cytokines, growth factors, erythropoietin, eicosanoids) or proteins and/or enzymes, and (*3*.) *clearance* of toxins, antigens, antigen-antibody complexes and purines. The phagocytosis and clearance of Kupffer cells is reduced through alcohol and drugs (e. g. mitomycin, α-methyldopa). (29, 53, 55, 62, 69) (s. p. 69) (s. figs. 2.8, 2.9)

3.3.3 Ito cells

Ito cells (T. Ito, 1951) are also known as fat-storing cells, hepatic stellate cells or lipocytes. These long-lived cells, 5−10 µm in size with long thin strands, lie in Disse's space (s. figs. 2.8, 2.9) and contain numerous cytoplasmic fat droplets as well as an abundance of vitamin A (= retinol ester). The retinol esters of the chylomicrons

are absorbed by the hepatocytes and hydrolyzed into retinol. The latter is either passed to the blood by means of RBP or transported to Ito cells and stored. In the fat droplets of Ito cells, about 75% of the liver retinoids are present in the form of retinol esters. These fat droplets are characteristic of Ito cells; they represent vacuolized cisterns of RBP. Ito cells constitute about 3–8% of the total liver cell number and 1.4% of the volume of the liver, occurring in a proportion of one Ito cell to 12–20 liver cells. Zone 3 of the acinus has the highest number. Ito cells are involved in the regulation of the width of the sinusendothelium, the microvascular tone and the regeneration of cells. They contain numerous filaments and organelles for protein synthesis, but cannot themselves produce RBP. Moreover, they are capable of transformation into myofibroblasts. Ito cells are able to synthesize and secrete collagen types I, III and IV, fibronectin, laminin, or other substances. Unlike fibroblasts, Ito cells can express desmin. Hence they may play an important part in fibrogenesis, particularly in pathological intralobular fibrosis. (4, 7, 16, 29, 55, 58, 70)

3.3.4 PIT cells

PIT cells were first demonstrated in the sinusoidal wall in rats (E. Witte et al., 1970). Later on, these lymphocytes with large granules and rod-cored vesicles were also found in the human liver, particularly in the sinusoids and in Disse's space. Due to their pseudopodia, they are variable. The proportion of PIT cells to Kupffer cells is 2:10. They are natural killer cells and destroy tumour cells or foreign cells as well as necrosed cells. It is not clear whether they have any additional "endocrine" function. Because of the strongly polarized distribution of their granulae, they could justifiably be classified as APUD cells. (6, 28, 29, 55, 65, 72)

3.4 Hepatocytes

► Hepatocytes were discovered by M.H. Dutrochet, who recognized "cellules vesiculaires agglomerées" in liver tissue in 1824. • This **first description** was confirmed and expanded by F. Kiernan (1833), J. Henle (1836) and J.E. Purkinje (1837) – they also discovered the liver cell nucleus.

Hepatocytes are **polygonal epithelial cells** with six or more faces corresponding to their individual position in the overall cell structure. The plate-like, overlapping hepatocyte formations build a three-dimensional system. With the reduction in weight of the liver from 3% to 2% relative to body weight with increasing age, there is also a corresponding decrease in the absolute number of hepatocytes. The usual life span of hepatocytes is at least 150–200 days; they perish as so-called *oncocytes* ("moulting"). This *programmed death* of the old hepatocytes is designated **apoptosis**. As yet, there is no reliable information available regarding the normal life span of human hepatocytes. It is determined on the one hand by genetic factors and on the other hand by exogenous factors, which differ in nature and scope of influence. In rats, a life span of 191 to 453 days was established for hepatocytes.

Proportion of liver volume	80%
Proportion of total cell number	60–65%
Number of liver cells	300 billion
Number of hepatocytes per g of liver	171 million
Diameter of hepatocytes	20–40 µm
Proportion of hyaloplasm in cell volume	54,9%
Lifespan of hepatocytes	150 (–200) days
Mitosis rate per 10,000–20,000 liver cells	1
Membrane surface of hepatocytes	33,000 m^2
and organelles (s. p. 26)	

Hepatocytes show a varying content of carrier, receptor and channel proteins. They have a clearly contoured cell membrane which is divided into three compartments defined by morphological and functional **cellular polarization.** (*1.*) About 37% of the external area of the hepatocyte membrane is *sinusoidal surface* (= basolateral) the absorptive and secretory function of which is increased sixfold by numerous microvilli; they lie in Disse's space. Some even protrude through the fenestrae into the sinusoids and thereby have direct contact with the blood. On the sinusoidal membrane, there are invaginations with vesicles underneath. (*2.*) About 15% of the outer hepatocyte membrane consist of canaliculi, termed *canalicular surface* (= apical). This area is the secretory pole of the cell. (*3.*) The remaining 50% of the external hepatocyte membrane constitute the smooth *intercellular fissure,* which is connected with Disse's space. This fissure is sealed from the canaliculi by *tight junctions* (= zonula occludens), allowing only an exchange of water and cations to take place. The adjacent adhesion areas of the neighbouring hepatocytes, the *intermediate junctions* (= zonula adhaerens) and the *desmosomes* (= macula adhaerens), are sealed by membrane proteins. These last two connecting structures are known collectively as adhering junctions. Thus, desmosomes link neighbouring hepatocytes, whereby the cytoskeleton is involved. They are distributed in an irregular fashion on the lateral membrane and help to stabilize the hepatocyte structure. Actually, they contain *gap junctions* (= maculae communicantes) which form tube-like connections between adjacent hepatocytes and so facilitate the intercellular exchange. When cell death occurs, the gap junctions of neighbouring cells, as dynamic structures, close down in order to prevent the progression of cell death. (s. figs. 2.8–2.10, 2.16)

Three **zonal areas** can also be differentiated in hepatocytes based on ultrastructural and functional differences (9, 32, 35, 59): (*1.*) *vascular zone* (supranuclear), (*2.*) *lateral zone*, and (*3.*) *biliary zone* (adjacent to the bile capillaries). • They each have a different stock of *organelles.* (s. p. 30)

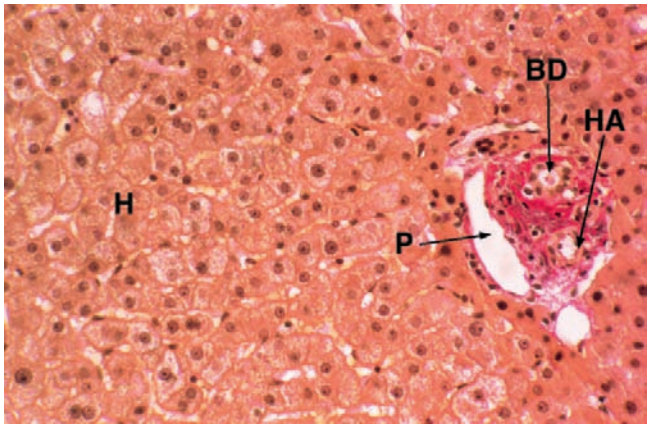

Fig. 2.10: Normal hepatic tissue. H = hepatocytes, P = portal vein, BD = bile duct, HA = hepatic arteriole (EvG)

3.5 Biliary epithelial cells

Biliary epithelial cells are organ-typical. They constitute some 3.5% of all hepatic cells. Depending on the size of the biliary ducts in which they are located, they show distinct histological and histochemical variations. In comparison with hepatocytes, biliary epithelial cells contain fewer mitochondria and less ER; there is a complete absence of cytochrome P 450. They are rich in cytoskeleton and contain Golgi apparatus and vesicles. The round-to-oval nuclei lie in the basal cytoplasm. These biliary cells probably play a role in biligenesis. (63) The epithelial cells of the intermediate ductules are also regarded as stem cells for the liver parenchyma.

4 Nervous system

The hepatic nerves consist of fibres of the sympathetic ganglia Th_5-Th_9 and the postganglionic fibres of the coeliac ganglion the vagus and the right phrenic nerve. At the porta hepatis, they form one plexus around the hepatic artery and another plexus around the portal vein plus biliary duct. With the vessels, the nerves reach the liver and "terminate" in the portal fields, where they regulate biliary and vascular structures. Also in the perisinusoidal space, there is a fine neural network which is in direct contact with hepatocytes and Ito cells. The nerves contain adrenergic (aminergic), cholinergic and peptidergic fibres; the function of peptidergic innervation is unknown. This most finely ramified hepatic nervous system influences haemodynamics, the metabolism of hepatic cells, and the motility of the biliary ducts. The liver parenchyma itself is not sensitive to pain as it contains no sensory nerves. The liver capsule and the falciform ligament are innervated by sensitive phrenicoabdominal branches of the phrenic nerve. (1, 5, 61) • *A transplanted and therefore* **denervated liver** *shows that innervation is not essential for the function of the organ. This remarkable phenomenon cannot yet be explained.*

5 Hepatic lobules and acinus

► The term **parenchyma** referring to the liver tissue was coined by Erasistratos. The **liver lobules** were first described in the pig in 1664 by J.J. Wepfer (using microscopic techniques) while the lobular structure was confirmed by M. Malpighi in 1666. The term **acinus** was coined by S.Th. Sömmering in 1796. • However, it was F. Kiernan (1833) who first gave a classic definition of the lobule in pig liver ("hepatic lobule"). Today, such anatomical clarity can only be found in the livers of the camel, polar bear and seal. (s. fig. 1.18)

► Kiernan's description of the acinus provided the basis for subsequent definitions, such as *"biliary lobule"* (Ch. Sabourin, 1888), *"portal unit"* (F.P. Mall, 1906), *"hepaton"* (R. Rössle, 1930) and *"synergid of the liver"* (H. Siegmund, 1943). In 1848 J. Gerlach had recognized that liver cells were arranged in bands (columns). • Not until a hundred years later did H. Elias (1949) describe the arrangement of liver cells in the form of plates as muralium simplex or lamina hepatis, with internal cavities (= lacunae). (11) (s. fig. 2.11) • E.H. Bloch (1970) considered the "single sinusoidal unit" to be a functional unit of the liver, the main component of which is a sinusoid lying sandwich-like between the hepatocyte trabeculae. • T. Matsumoto et al. (1979) suggest an angioarchitectural concept. The portal corner region with septal ramifications is seen as the basic structure of the primary hepatic lobule. In the parenchyma, *vascular septa* are postulated, i.e. terminal ramifications of the portal vein which join up with the sinusoids directly. (In 1997, W. Ektaksin et al. described them as inlet venules.) (s. fig. 2.12)

Total number of hepatic lobules	1.0–1.5 million
Depth of hepatic lobules	1.5–2.0 mm
Diameter of hepatic lobules	1.0–1.3 mm

5.1 Central vein lobule

The classic central vein lobule accords with the traditional description of *lobular structure* (F. Kiernan, 1833; H. Eppinger, 1937; H. Elias, 1949). The hepatic lobule resembles a hexagon with portal tracts at the corners. It consists of radially arranged columns (or plates) of 15–25 liver cells placed between the limiting lamellae and the central vein, the axis of which they are also aligned with. This particular arrangement of the hepatocyte plates does not occur until after birth and is due to the suction effect of the right ventricle. The lobule is limited by the surrounding periportal fields. The hollow spaces between the liver cell plates form a labyrinth, in which the sinusoids and Disse's space are located. The *limiting plate* (W.H. Harris, 1942) or *limiting lamella* (H. Elias, 1949) consists of smaller, basophilic and glycogen-free liver cells with a nucleus which is richer in chromatin. As a unicellular liver plate, it lies perpendicular to the remaining liver cell plates. It is penetrated only by capillaries. As it is limited on the periportal side by Mall's space, it can only be reached by peripheral sinusoidal blood on the lobular side. Due to its optimal blood supply, the limiting plate proves itself to be a particularly resistant layer of liver cells. It constitutes a dividing wall between parenchyma and mesenchyma. This lobular structure thus shifts the periportal fields with the sup-

plying branches of the hepatic artery and portal vein to the periphery and the central vein to the centre of the lobule, which results in centripetal blood flow. The bile flows centrifugally towards the periphery. (s. figs. 1.18; 2.11–2.13)

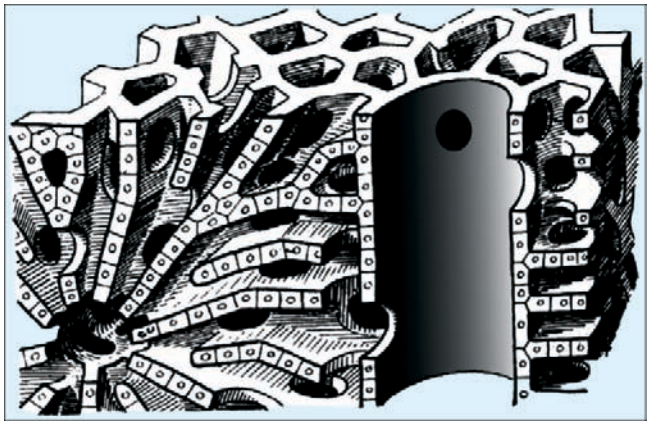

Fig. 2.11: Diagram of the traditional ("classic") hepatic lobule according to the lobular structure (F. Kiernan, 1833) (s. fig. 1.18) and as stereogram (H. Elias, 1949): the liver cell columns run radially from the limiting plate to the central vein (11) (s. fig. 2.16)

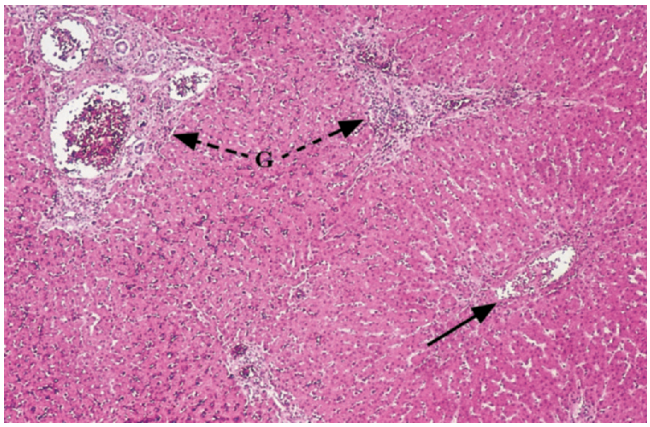

Fig. 2.12: Hepatic lobules with central vein (↑) and Glisson's triangles (G ---→). Slight distortion of the lobular architecture (HE)

5.2 Portal vein lobule

The portal vein lobule was first recognized in the description of the "portal unit" given by F.P. Mall (1906). It resembles a hexagon. The periportal field constitutes the axis at the centre while the central veins form the limiting points. (s. fig. 2.13) The glandular character of the liver is the main criterion of differentiation of the portal vein lobule. Thus the direction of blood flow is from the centre towards the periphery (centrifugal) and the direction of bile flow from the periphery towards the centre (centripetal). It could also be demonstrated that the lobule periphery is enclosed by basket-like ramifications of the portal vein (= *corbicula portalis*). (74) This further emphasizes the significance of the hepatic lobule.

5.3 Liver acinus

The functional and microcirculatory hepatic unit forms the basis for assessing the hepatic acinus (A.M. Rappaport, 1954). (40–42) The portal vascular bundle, with the terminal branches of the hepatic artery and portal vein diverging fan-shaped after penetrating the lobules, is at the centre of the *acinar structure.* These vessels represent the central axis for the circular blood supply of the related liver parenchyma. This area is roughly the shape of a rhombus, the outer angles of which are formed by the two *central veins* of the adjacent lobules while the diagonal corresponds to the (arterial and portal) *terminal vessels.* The central vein at the periphery of the acinus, to which the sinusoids extend radially, drains off the venous blood; it is generally known as the *terminal hepatic venule* (= terminal hepatic vein). (s. p. 21) The liver acinus also serves as *secretory unit* for the transport of bile. In the acinus, the blood flow occurs centrifugally and the flow of bile centripetally. Three or more acini together form a so-called complex acinus. • This zonal model has been modified according to more recent findings, so that zones 1 to 3 do not surround the terminal afferent vessels in an onion-like way, but are now arranged in circular form around the vessels. (31) (s. figs. 2.13–2.15)

The zones of the acinus differ in their blood supply, corresponding to the distance of the hepatic cells from the periportal field and terminal blood vessels respectively. **Zone 1** has the best supply of oxygen and substrates; it comprises the (lobule-peripheral) parenchyma adjacent to the limiting lamella. Toxins are most damaging in zone 1. **Zone 2** corresponds to the intermediate area with a reduced supply of blood. **Zone 3,** which has the poorest blood supply, is located near the central vein, i.e. at the end of the microcirculatory system of the liver. Having the lowest oxygen supply, this area has the least resistance to damaging influences, e.g. oxygen deficiency, and it has the lowest regenerative capacity. It has also been postulated that the two halves of zone 2 can be added to zones 1 and 3 respectively, because zone 2 has no separate functional boundaries of its own. (18) • **Zones A, B, C** form concentric circles round the periportal field, which have a similarly decreasing quality of blood supply. Thus zone C1 is better supplied than, for example, C3, A2 or A3, i.e. the optimal blood supply does not only depend on proximity to the periportal field, but also on proximity to the terminal distributory branches of the blood vessels or to the limiting lamella. (s. figs. 2.13–2.15)

In correspondence with the oxygen gradient in zones 1 to 3 and A to C, there is a metabolic and enzymatic "zoning" of the hepatocytes. W. Eger had already described "functional zones" in 1954. (10) They have subsequently undergone reclassification as acini, although they were initially considered to be part of the lobular structure. This chemomorphology of the acinus is designated the **metabolic heterogeneity** of hepatocytes (K. Jun-

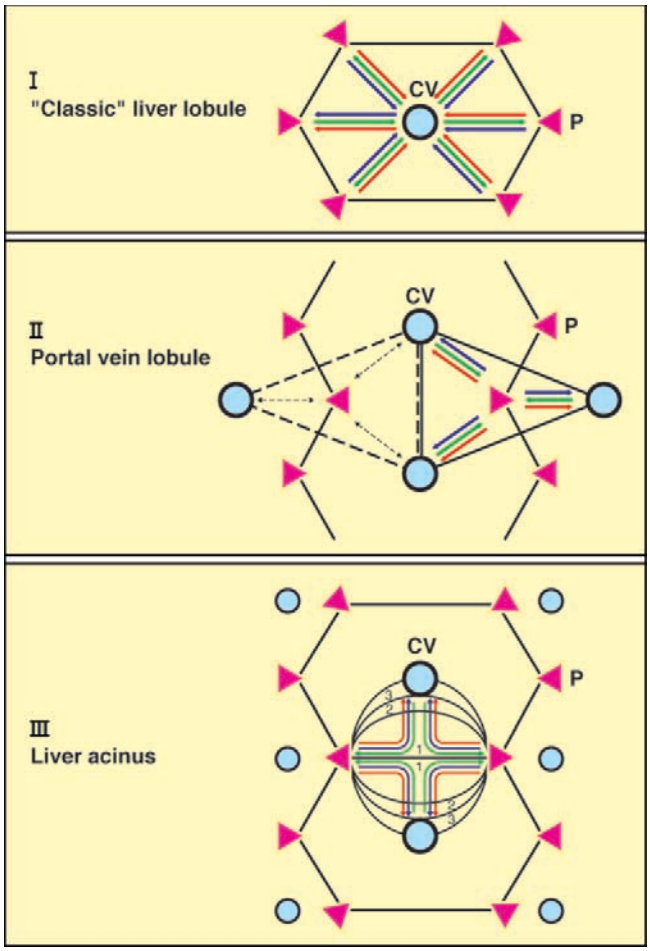

Fig. 2.13: Diagram of the classic hepatic lobule (I), the portal vein lobule (II) and the hepatic acinus (III): CV = central vein (○), P = portal tract (▶). Flow direction: venous blood (= blue arrow), arterial blood (= red arrow) and bile (= green arrow), with the microcirculatory acinus zones 1, 2, 3. • (cf. W. Ekataksin et al., 1992: the microvascular unit is regarded as an area in which all liver cells receive blood from a common terminal vessel)

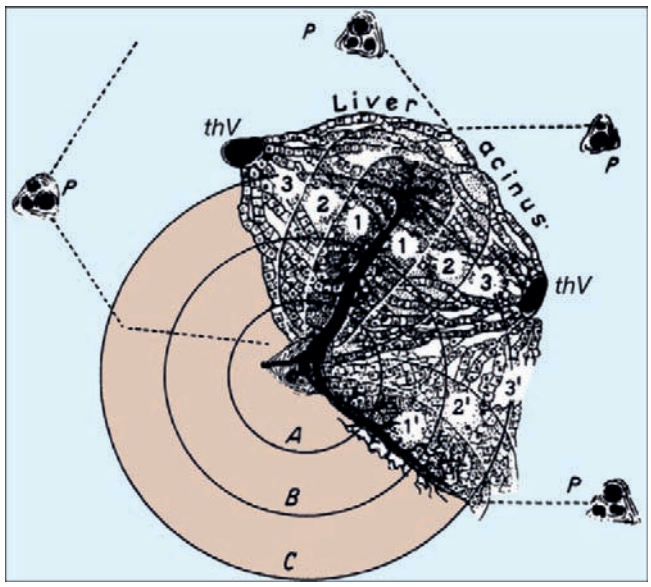

Fig. 2.14: Diagram of the functional (microcirculatory) liver unit ("simple acinus") (A. M. Rappaport, 1960, 1963): terminal hepatic vein (thV), periportal field (P), zones of different blood supply A, B, C and 1, 2, 3. Zone 1 (afferent zone): zone richest in O_2, nutrients and hormones. Zone 3 (efferent zone): zone poorest in O_2, nutrients and hormones, but enriched with CO_2 and metabolites from zones 1 and 2. (Direction of blood flow is from 1 to 3 and from A to C)

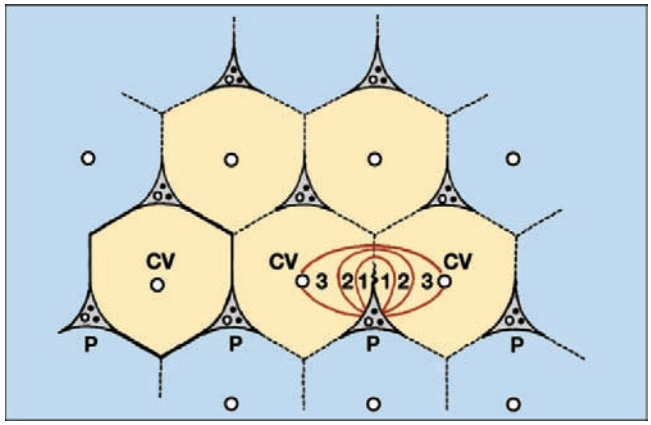

Fig. 2.15: Diagram of the liver lobule and the acinus arranged like a clover leaf around the portal field according to the acinar structure (modified from D. Sasse, 1986): central hepatic vein (CV) or terminal hepatic vein, periportal field (P). Circulatory and metabolically different zones: zone 1 (periportal), zone 2 (intermediate), zone 3 (perivenous)

germann et al., 1978). (15, 18, 26, 27, 31, 63) (s. p. 36) Thus different metabolic processes are found in the periportal region (zone 1) and in the perivenous area (zone 3). Additionally, zones 1 to 3 are equipped with a very varied stock of enzymes, which does not, however, remain constant. There is also an **ultrastructural heterogeneity.** In zone 1, Kupffer cells, microvilli, mitochondria, lysosomes and the Golgi structures are more numerous than in zone 3, and the lumen of the bile capillaries is larger. (35) By contrast, there is less smooth endoplasmic reticulum in zone 1 than in zone 3 (15,700 μm^3 against 21,600 μm^3 per cell). The fenestration of the sinus-endothelium increases continuously from zone 1 to zone 3. (24) • Enzyme content and metabolic capacity of the hepatocytes depend on *microcirculatory variability* (caused endogenously or exogenously) and can vary considerably in the individual acinus areas.

Strong arguments have, however, been put forward against metabolic heterogeneity, at least against the concept of rigid zoning. The columns of the hepatocytes in the separate zones proved to be variable with regard to staining characteristics as well as enzyme content. Surprisingly, it could be unequivocally shown that a clear cellular multiplication occurs in the peripheral, i.e. in the periportal, zone and that the hepatocytes formed here are displaced towards the central vein. The hepatocytes migrate through all three zones at a speed of 1.44 µm/day, which is 0.32% of the diameter of the acinus *("streaming liver")*. (77) From this it can be established that hepatocytes adopt the respective zonal differentia-

tion during their migration from zone 1 to zone 3 and that the individual hepatocyte also receives the complement of enzymes typical for the respective zones during its spatial displacement. • With regard to their *metabolic capacities*, hepatocytes are thus pluripotent: their zonal position, the variability of microcirculation and their ability to migrate interzonally may possibly decide which metabolic functions are fulfilled directly and which are "deferred" from zone to zone.

The morphological unit is the **liver lobule.** With regard to the histological evaluation of a liver biopsy specimen, the use of this *lobular structure* is imperative to pathologist and clinician alike.

On the basis of the acinar concept, the **liver acinus** can be seen as a *"structural + microcirculatory + functional unit"*, which is nevertheless subject to the blood flow and the variability of the same.

6 Subcellular structures

Liver cells comprise the cell nucleus (= *karyoplasm*) and the cell body (= *cytoplasm*). Hepatocytes and sinusoidal cells have various types of *organelles* in their eosinophilic cytoplasm, such as endoplasmic reticulum, Golgi apparatus, lysosomes, mitochondria, peroxisomes, ribosomes, centrioles and kinetosomes. Numerous and diverse metabolic processes take place with their help. Almost all cytoplasmic structures of liver cells are continuously renewed (up to twice daily). (23, 28, 32, 35, 46, 50, 55) (s. figs. 2.9, 2.16–2.18) (s. tab. 2.1)

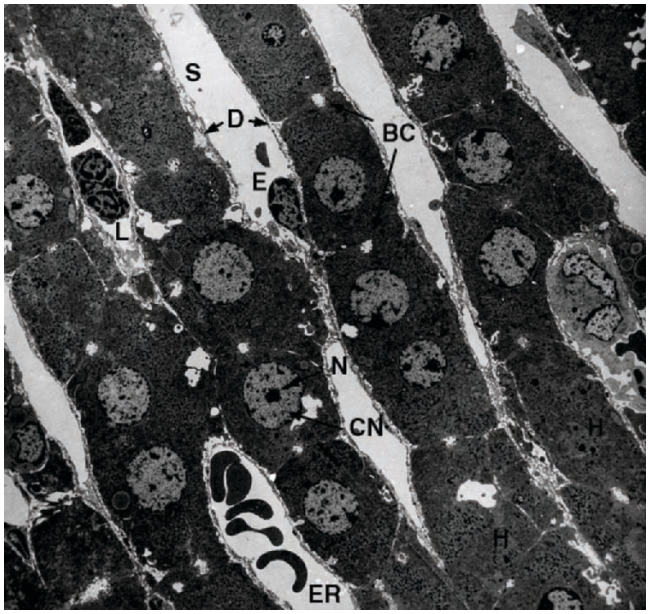

Fig. 2.16: Hepatocytes (H) in the form of cellular trabeculae with biliary capillaries (BC), cell nucleus (CN) and nucleolus (N); sinusoids (S) with leucocyte (L), endothelial cell (E) and erythrocytes (ER); Disse's space (D); × 1,980 (s. figs. 2.10–2.12)

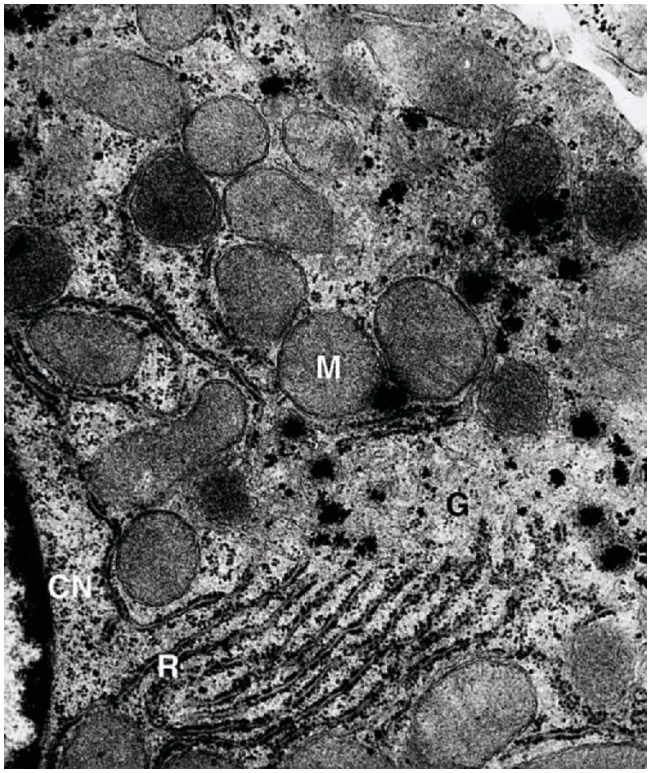

Fig. 2.17: Hyaloplasm of the hepatocyte: glycogen granules (G), mitochondria (M), rough endoplasmic reticulum with ribosomes (R); edge of the cell nucleus (CN); × 32,000 (s. fig. 2.9)

6.1 Cytoplasm

The cytoplasm of the cell is designated *hyaloplasm* in electron microscopy and *cytosol* in biochemistry. It constitutes about 51% of the cell volume and shows a microtubular lattice. (s. fig. 2.17) Basophilia, caused by ribonucleic acid, is the histochemical index for increased functional activity of the hepatocytes. The smooth endoplasmic reticulum is responsible for the pale eosinophilic colouring of the cytoplasm. Together with the cell membrane, the hyaloplasm is also involved in the formation of microvilli, pseudopodia, etc. • The watery solution of the hyaloplasm contains a mixture of molecular components. Of these, the proteins with about 10,000 different forms (15–20% of the weight, 10 billion protein molecules) are by far the most important. Further, glycogen granula in high numbers as well as pigments and lipid droplets can be found. Water loss from the hepatocytes gives rise to so-called *dark liver cells* (= shrinkage, with catabolic signal); conversely, water retention gives rise to so-called *hydropic liver cells* (= swelling, with anabolic signal). Indeed, the latter term cannot really be defined as such since numerous changes in the cells are involved.

6.2 Cell nucleus

The nucleus of the liver cell has one or two nucleoli. (s. fig. 2.18) Its proportion of the cell volume is 6%. About 20–25% of liver cells have two nuclei, presumably as a sign of increased cell activity. Number, size, nuclear pat-

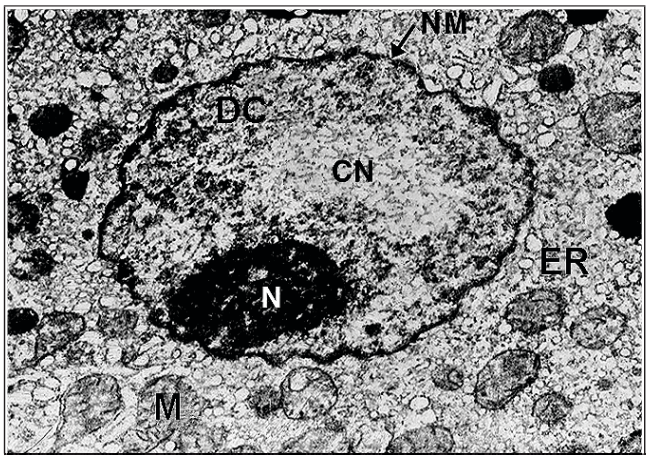

Fig. 2.18: Nucleus, nucleolus and hyaloplasm of the liver cell (20): cell nucleus (CN), marginal nucleolus (N), electron-dense dark nuclear capsule (DC), undulating nuclear membrane with (partial) fusion of the two membranes (NM), endoplasmic reticulum (ER), mitochondria (M); × 14,600

tern or nuclear changes are very varied due to diverse influences (e.g. age, nutrition, physiological "moulting") − above all in pathological processes. About 10−44% of the nuclei are diploid, 55−80% are tetraploid and 5−6% are octoploid. Increasing polyploidy is deemed a precancerous phase. The nucleus has a bilaminar "nuclear membrane" (D.W. Fawcett, 1955). The inner nuclear membrane is connected to the heterochromatin, while the outer layer is joined via membrane eversions to the endoplasmic reticulum it is covered with ribosomes. Between the two membranes is the 20−70 nm wide perinuclear cavity, which is connected to the spatial system of the rough endoplasmic reticulum. • The inner structure of the nucleus is non-homogeneous due to granules and the thread-like form of the chromatin; the latter constitutes the main component of the nucleus. This comprises chromosomes which contain genetic information in the form of DNA (deoxyribonucleinic acid). With approx. 3 x 10^9 nucleotides per nuclei, this information is incredibly tightly packed. The DNA is firmly attached to histones (nucleosomes). RNA transcription occurs in the interphase nucleus, and DNA is reduplicated prior to cell division. In the metabolically activated nucleus, RNA substances are concentrated in the nucleolus, in which the ribosomes are synthesized. It is chiefly the non-activated, non-despiralized chromatin in the form of heterochromatin which is deposited in the nuclear periphery, so that a dark nuclear capsule can be differentiated. Number and size of the nucleoli are dependent upon various influences. The exchange of substances and the transfer of genetic or metabolic information between nucleus and cytoplasm occur predominantly through (*1.*) diffusion, (*2.*) cell membrane pores (diameter ca. 10 nm), and (*3.*) pinocytosis.

6.3 Organelles

Various tiny structures, so-called organelles, are embedded in the cytoplasm, where they make numerous cell functions possible. (s. fig. 2.9) (s. tab. 2.1) • The enzyme-

	Membrane surface in proportion to total hepatocyte membrane surface	Proportion of hepatocyte cell volume	Number per hepatocyte	Function
1. Rough endoplasmic reticulum (RER)	35%	13%	1	Synthesis of proteins, glucose-6-phosphatase, triglycerides, coagulant factors, *etc.*
2. Smooth endoplasmic reticulum (SER)	16%	7,7%	1	Biotransformation; synthesis of steroid hormones, phospholipids, bilirubin conjugation, cholesterol, bile acids, glucose metabolism, *etc.*
3. Golgi apparatus	7%			Secretion of lipoprotein, bile acids, glycoprotein synthesis, protein glycolization
4. Mitochondria	39%	18−22%	1,700−2,200	Protein secretion, haem synthesis, transport and degradation functions, cellular energy generation (ATP), oxidative phosphorylation, urea synthesis, gluconeogenesis, liponeogenesis, ketogenesis, β-oxidation of fatty acids, citric acid cycle, respiratory chain, *etc.*
5. Lysosomes	0.4%	2%	200−300	Degradation of "foreign" macromolecules in the cell by means of hydrolytic enzymes, deposition of copper, ferritin, lipofuscin, bile pigment, *etc.*
6. Peroxisomes	0.4%	1,3%	400−1,000	Oxidative degradation processes by means of peroxidases, catalase, xanthine oxidase, degradation of long-chain fatty acids, antioxidative function, bile acid synthesis, alcohol metabolism, purine metabolism, *etc.*

Tab. 2.1: Numerical and functional summary of the most important organelles (adapted from B. Alberts et al., 1983) (s. figs. 2.9, 2.17)

rich **mitochondria** have an outer and an inner membrane, with the latter forming creases (= cristae). The outer membrane is relatively permeable for small molecules. However, the inner membrane (which surrounds the matrix) must use specific transport proteins to enable protons, calcium, phosphate and so on to pass. Energy-rich substrates are transformed into ATP in the mitochondria. The enzymes which are responsible for fatty-acid degradation and the citric-acid cycle can be found in the matrix. The inner membrane also contains the enzymes of the so-called respiratory cycle. An enormous number of energy-providing reactions and metabolic processes take effect at this site. They have a round-to-oval shape with a diameter of about 1 µm. There are 1,000(−2,200) mitochondria per liver cell (18−22% of the liver cell volume). They generally lie in the vicinity of the rough ER and are able to move within the cell. Multiplication occurs through division. Their half-life is 9−10 days. (s. figs. 2.17, 2.18) • The **endoplasmic reticulum** (= about 20% of the liver cell volume) consists of a smooth (SER) (40%) and a rough (RER) (60%) portion. The rough surface is due to ribosomes (9−10 million/liver cell); it is also known as ergastoplasm (identical to the basophilic granulae). (s. fig. 2.17) The SER contains microsomes. It forms tubules and vesicles as well as being the site of the cytochrome P 450 systems. • The **Golgi complex** is generally found between the cell nucleus and the canaliculus and consists of four to six cisternae. This membrane system, which is formed from lamellar vesicles, communicates with the smooth ER. It is primarily concerned with the intracellular transport of various substances, but also with processes of degradation and excretion. • The **lysosomes** (200−300/liver cell) lie predominantly close to the canaliculus. They are organelles for the digestion and storage of cellular and noncellular (also exogenous) material. Lysosomes contain hydrolytic enzymes, mainly proteases (= lysosomal enzymes) and acid phosphatase. • The **peroxisomes** (= microbodies) are enzyme-rich and oxidative-reactive structures. They are round to oval in shape and 0.2−1.0 µm in size. The liver cell contains 400−1,000 peroxisomes.

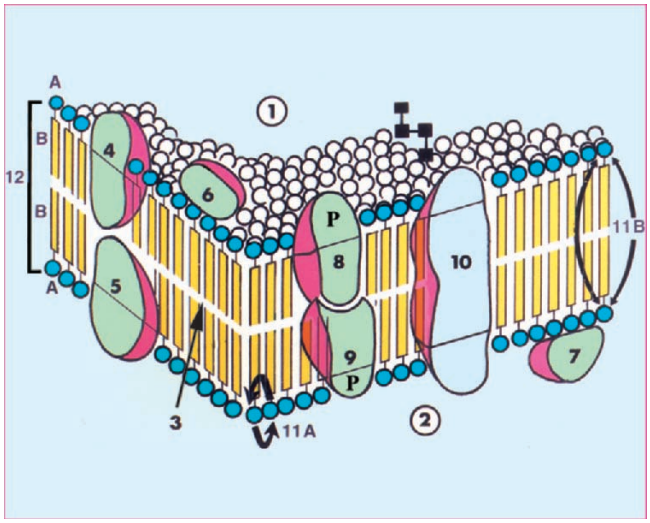

Fig. 2.19: Diagram of the plasma membrane showing its integral proteins (fluid mosaic model) (adapted from S.J. Singer et al., 1972 and H. Knüfermann, 1976). • 1: external aqueous milieu, 2: internal aqueous milieu, 3: fracture plane of the apolar membrane layer, 4: externally orientated intrinsic protein (ectoprotein), 5: internally orientated intrinsic protein (endoprotein), 6: external extrinsic protein, 7: internal intrinsic protein, 8, 9: membrane-penetrating proteins with hydrophobic interactions in the inside of the membrane (P = polar region), 10: membrane pervaded by glycoprotein with sugar residues (■-■-), 11: lateral diffusion (A) and flip-flop (B), 12: hydrophilic region (A) and hydrophobic region (B) of the bilayer membrane

6.4 Membrane

Hepatocytes, like the essential organelles, are surrounded by membranes which differ in their function and structure. The membrane of the hepatocytes consists of lipids (52−54%), proteins (44−46%) and carbohydrates (2−4%). The latter are structural, antenna-like docking points for tissue-specific receptors. (s. fig. 2.19) The membrane surface area of 3×10^5 million liver cells and their organelles is 33,000 m^2, i.e. *a surface area that is 5 times larger than that of a football field* (inner membrane surface area = 24,000 m^2). • The basolateral (sinusoidal) proportion of the hepatocyte membrane amounts to approx. 85%, the apical (canalicular) proportion to approx. 15%. • The membranes consist of a double layer (bilayer) of choline phospholipids, into which cholesterol, proteins, glycolipids and glycoproteins are incorporated with "systematic variability". This specific structure makes possible the enormous number of membrane-related functions. The hydrophilic parts of the phospholipid molecules form the outer and inner boundaries of the membrane, while the hydrophobic parts are directed towards its interior. The bilayer membrane is a liquid crystalline system (= *fluidity of the membrane*) allowing lateral movement (= *lateral diffusion*) of the proteins and phospholipids deposited in this area. In addition, the phospholipids can change position between the layers (= *flip-flop*). (71) The side of the sinusoidal cell turned towards the hepatic lacuna carries numerous microvilli, increasing the surface area of the cell membrane. (48) The form and number of the microvilli not only depend upon the functional condition of the liver cell, but also upon damaging effects. • The hepatocyte membrane has multiple and existential *functions* such as (*1.*) mechanical and chemical protection, (*2.*) demarcation of neighbouring cells, (*3.*) link with the extracellular matrix, (*4.*) contact and interaction with neighbouring cells, (*5.*) signal exchange between intracellular and extracellular space, (*6.*) transport mechanisms, (*7.*) enzymatic reactions, (*8.*) anchoring of the cytoskeleton.

6.5 Cytoskeleton

The cytoskeleton, made up of protein fibres, consists of dynamic structures with the ability to adapt their form rapidly to any respective requirements. It is important for the overall organization of the cell (e. g. transport processes, organelle movement, cell polarity, and cell division). The cytoskeleton comprises the following *components:* (*1*.) actin filaments, (*2*.) microtubules, and (*3*.) intermediate filaments. (12) (s. fig. 2.9)

Thread-like **actin filaments** (microfilaments) spread through the hepatocytes, creating a three-dimensional network and ensuring both form and stability of the cell. They also guarantee the shape of the microvilli and fenestrae as well as supporting the mechanical functions of the canaliculi. In addition, they influence the viscosity of the cytoplasm. Cytochalasin A depolymerizes actin with lumen enlargement of the canaliculi, thus causing cholestasis; in this way phalloidin both stabilizes and inhibits the bile flow. • The tube-like **microtubules** consisting of tubulin also form a network within the cell. They serve the targeted transport of subcellular substrates or organelles, and they are important for the mitotic mechanisms involved in cell division. • The **intermediate filaments** also have a tubular structure and, in addition to their stabilizing functions, probably serve the intracellular transport of materials, too. • **Microtrabeculae** have also been postulated (possibly as a special form of actin filaments), forming a three-dimensional cytoplasmic meshwork, in which enzymes may also be deposited. The microtrabeculae form a dynamic lattice and in this way are connected with all organelles, microtubules and filaments as well as with the nuclear and cellular membranes. Various "motor proteins" produce a diverse range of motilities at the cellular and subcellular level. • This gives rise to the **cytoplast,** the vital functional unit of the liver cell.

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