SHERLOCK'S DISEASES OF THE LIVER AND BILIARY SYSTEM

13TH EDITION

with website

Edited by

James Dooley | Anna Lok
Guadalupe Garcia-Tsao | Massimo Pinzani

WILEY Blackwell

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The website includes:

- PowerPoints of all figures from the book for downloading

Sherlock's Diseases of the Liver and Biliary System

Thirteenth Edition

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Preface to the Thirteenth Edition

Since 2011 important new data have contributed to all areas of hepatobiliary disease, and revision of the 12th edition of *Sherlock's Diseases of the Liver and Biliary System*, published then, is timely. Many clinical challenges remain. However, advances in the understanding of pathogenesis and prognostic staging are leading to more individualized patient care and providing improved outcomes in many conditions. Studies of the basic cellular mechanisms involved are leading to the investigation of new therapeutic approaches.

A particular advance with important implications is in the treatment of hepatitis C, which can now be cured in more than 95% of patients with 8 to 16 weeks of oral antiviral therapy.

The current hepatological epidemic in the Western world is non-alcoholic fatty liver disease and much research is published and on-going to dissect and understand the mechanisms and predisposing factors related to progression to cirrhosis. New agents are being studied for their potential to prevent or reverse such progression.

The drive of clinical hepatologists and basic scientists for greater understanding is a credit to the worldwide community of those involved. International collaborations to gather data on large cohorts of patients are playing an important role. Viral hepatitis has been mentioned, but there has been much new work in cholestatic liver diseases. Molecular genetic techniques are more accessible, for example in the diagnosis of conditions such as haemochromatosis and Wilson disease. Gene therapy may be on the horizon for some genetic diseases. Genome-wide studies are becoming almost routine to dissect the predisposing factors, for example in immune-related and alcoholic liver disease. Liver imaging, already strides ahead of what was available in earlier days, has greatly reduced the need for biopsies. Liver transplantation is widely available. The selection and management of this cohort of patients is constantly being assessed and refined to attain better outcomes.

Sheila Sherlock, an enthusiastic pioneer in the development of Hepatology worldwide, would have been excited and we think stunned by the current state of her speciality. She herself used her textbook as a resource in which to annotate the most current work and knowledge. Her goal with each edition was to provide a textbook of manageable size, critical and current.

It is with this ethos that we have approached the 13th edition with specialist contributors from across the world. We hope that this edition will stimulate interest in hepatobiliary disease among students and young doctors, as well as provide a reference source for specialist hepatologists, surgeons, pathologists, radiologists, and clinical nurse specialists. The edition has over 100 new figures and more than 1500 new references.

The format is as before – designed to preserve clarity, with the text written as far as is possible with Sheila Sherlock's style in mind.

New chapters reflect current developments and interest with particular contributions on non-invasive assessment of hepatic fibrosis and cirrhosis, coagulation in cirrhosis, and nutrition in the patient with cirrhosis.

We are most grateful to the authors for their work updating, fully revising, or providing new chapters. We thank Pri Gibbons and Deirdre Barry at Wiley Blackwell for their contributions to making this project a success. We wish also to express our particular thanks to Gill Whitley for her unflinching commitment, expertise, and support during the production of this 13th edition. We are grateful to Jane Fallows for the new artwork and for the reworking where necessary of figures from the previous edition.

Finally, this textbook is the legacy of Sheila Sherlock's exceptional life and career, and we hope that her daughters and their families will take pleasure in seeing their mother's seminal contribution to Hepatology celebrated in another edition of *Diseases of the Liver and Biliary System*.

September 2017

James S. Dooley
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Preface to the First Edition

My aim in writing this book has been to present a comprehensive and up-to-date account of diseases of the liver and biliary system, which I hope will be of value to physicians, surgeons, and pathologists and also a reference book for the clinical student. The modern literature has been reviewed with special reference to articles of general interest. Many older more specialized classical contributions have therefore inevitably been excluded.

Disorders of the liver and biliary system may be classified under the traditional concept of individual diseases. Alternatively, as I have endeavoured in this book, they may be described by the functional and morphological changes which they produce. In the clinical management of a patient with liver disease, it is important to assess the degree of disturbance of four functional and morphological components of the liver: hepatic cells, vascular system (portal vein, hepatic artery, and hepatic veins), bile ducts, and reticulo-endothelial system. The typical reaction pattern is thus sought and recognized before attempting to diagnose the causative insult. Clinical and laboratory methods of assessing each of these components are therefore considered early in the book. Descriptions of individual diseases follow as illustrative examples. It will be seen that the features of hepatocellular failure and portal hypertension are described in general terms as a foundation for subsequent discussion of virus hepatitis, nutrition liver disease, and the cirrhoses. Similarly blood diseases and infections of the liver are included with the reticuloendothelial system, and disorders of the biliary tract follow descriptions of acute and chronic bile duct obstruction.

I would like to acknowledge my indebtedness to my teachers, the late Professor J. Henry Dible, the late Professor Sir James Learmonth and Professor Sir John McMichael, who stimulated my interest in hepatic disease, and to my colleagues at the Postgraduate Medical School and elsewhere who have generously invited me to see patients under their care. I am grateful to Dr A. G. Bearn for criticizing part of the typescript and to Dr A. Paton for his criticisms and careful proof reading. Miss D. F. Atkins gave much assistance with proof reading and with the bibliography. Mr Per Saugman and Mrs J. M. Green of Blackwell Scientific Publications have co-operated enthusiastically in the production of this book.

The photomicrographs were taken by Mr E. V. Willmott, FRPS, and Mr C. A. P. Graham from sections prepared by Mr J. G. Griffin and the histology staff of the Postgraduate Medical School. Clinical photographs are the work of Mr C. R. Brecknell and his assistants. The black and white drawings were made by Mrs H. M. G. Wilson and Mr D. Simmonds. I am indebted to them all for their patience and skill.

The text includes part of unpublished material included in a thesis submitted in 1944 to the University of Edinburgh for the degree of MD, and part of an essay awarded the Buckston–Browne prize of the Harveian Society of London in 1953. Colleagues have allowed me to include published work of which they are jointly responsible. Dr Patricia P. Franklyn and Dr R. E. Steiner have kindly loaned me radiographs. Many authors have given me permission to reproduce illustrations and detailed acknowledgments are given in the text. I wish also to thank the editors of the following journals for permission to include illustrations: *American Journal of Medicine, Archives of Pathology, British Heart Journal, Circulation, Clinical Science, Edinburgh Medical Journal, Journal of Clinical Investigation, Journal of Laboratory and Clinical Investigation, Journal of Pathology and Bacteriology, Lancet, Postgraduate Medical Journal, Proceedings of the Staff Meetings of the Mayo Clinic, Quarterly Journal of Medicine, Thorax*, and also the following publishers: Butterworth's Medical Publications, J. & A. Churchill Ltd, The Josiah Macy Junior Foundation, and G. D. Searle & Co.

Finally I must thank my husband, Dr D. Geraint James, who, at considerable personal inconvenience, encouraged me to undertake the writing of this book and also criticized and rewrote most of it. He will not allow me to dedicate it to him.

SHEILA SHERLOCK
1955

Chapter 1

Anatomy and Function

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LEARNING POINTS

- The liver is derived from a foregut endodermal bud which develops in the third week of gestation and divides into two parts: hepatic and biliary.
- The Couinaud classification subdivides the liver into eight segments (segments I–IV in the left lobe, segments V–VIII in the right lobe) based on vascular and biliary anatomical landmarks.
- The lobule described by Kiernan is the most widely used unit of liver microanatomy, consisting of a hexagon-like region of liver parenchyma with a central vein as its hub and portal tracts located in the periphery of the hexagon.
- Hepatocytes are functionally heterogeneous within the lobular parenchyma, whereby centrilobular cells subserve different functions (e.g. drug metabolism) from periportal cells (e.g. bile salt-dependent bile formation).
- Uncomplicated regeneration of hepatocytes and/or bile duct epithelium usually occurs by cell division of the indigenous cells; however, when normal regenerative capacity is overwhelmed there may be activation of progenitors cells located in the region of the canals of Hering.

Development of the liver and bile ducts

The liver begins as a hollow endodermal bud from the foregut (duodenum) during the third week of gestation. The bud separates into two parts: hepatic and biliary. The *hepatic* part contains bipotential progenitor cells that differentiate into hepatocytes or ductal cells, which form the early primitive bile duct structures (bile duct plates). Differentiation is accompanied by changes in cytokeratin type within the cell [1]. Normally, this collection of rapidly proliferating cells penetrates adjacent mesodermal tissue (the septum transversum) and is met by ingrowing capillary plexuses from the vitelline and umbilical veins, which will form the sinusoids. The connection between this proliferating mass of cells and the foregut, the *biliary* part of the endodermal bud, will form the gallbladder and extrahepatic bile ducts. The intrahepatic bile ducts begin to develop at week 8 from the flattened epithelium of the ductal plates adjacent to portal tracts [2]. Bile begins to flow at about the 12th week. Connective tissue cells of portal tracts are derived from the mesoderm of the septum transversum. Kupffer cells derive from circulating monocytes and possibly yolk sac macrophages. Hepatic stellate cells appear to be mesodermal derivatives from submesothelial cells located beneath the surface of the developing liver [3]. The fetal liver is the main site of haemopoiesis by the 12th week; this subsides in the fifth month coincident with the onset of bone marrow haemopoietic activity, so that only a few haemopoietic cells remain at birth.

Anatomy of the liver

The liver, the largest organ in the body, weighs 1200–1500 g and comprises one-fiftieth of the total adult body weight. It is relatively larger in infancy, comprising one-eighteenth of the birth weight. This is mainly due to a large left lobe.

Sheltered by the ribs in the right upper quadrant, the upper border lies approximately at the level of the nipples. There are two anatomical lobes, the right being about six times the size of the left (Fig. 1.1, Fig. 1.2, Fig. 1.3). Lesser segments of the right lobe are the *caudate lobe* on the posterior surface and the *quadrate lobe* on the inferior surface. The right and left lobes are separated anteriorly by a fold of peritoneum called the falciform ligament, posteriorly by the fissure for the ligamentum venosum, and inferiorly by the fissure for the ligamentum teres.

The liver has a double blood supply. The *portal vein* brings venous blood from the intestines and spleen and the *hepatic artery,* coming from the coeliac axis, supplies the liver with arterial blood. These vessels enter the liver through a fissure, the *porta hepatis,* which lies far back on the inferior surface of the right lobe. Inside the porta, the portal vein and hepatic artery divide into branches to the right and left lobes, and the right and left hepatic bile ducts join to form the common hepatic duct. The *hepatic nerve plexus* contains fibres from the sympathetic ganglia T7–T10, which synapse in the coeliac plexus, the right and left vagi and the right phrenic nerve. It accompanies the hepatic artery and bile ducts into their finest ramifications, even to the portal tracts and hepatic parenchyma [4].
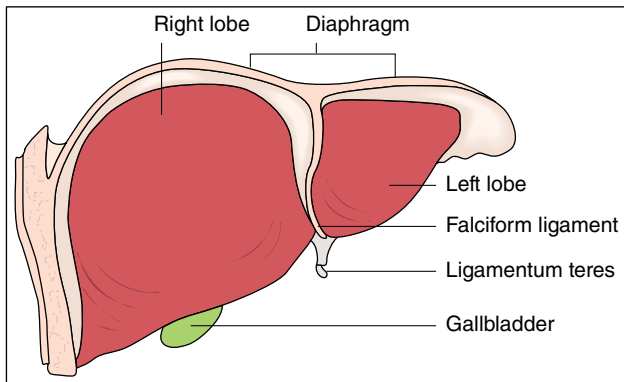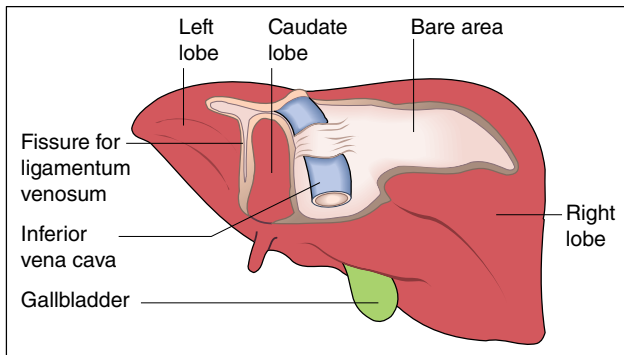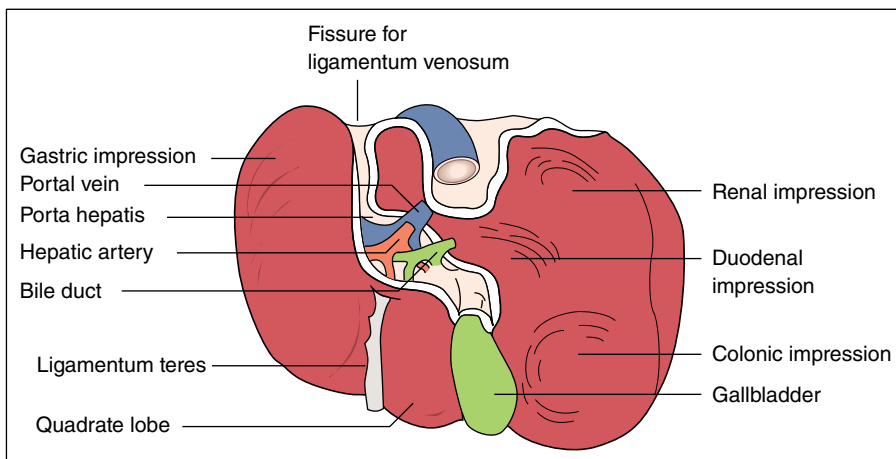
The *ligamentum venosum,* a slender remnant of the ductus venosus of the fetus, arises from the left branch of the portal vein and fuses with the inferior vena cava at the entrance of the left hepatic vein. The *ligamentum teres,* a remnant of the umbilical vein of the fetus, runs in the free edge of the falciform ligament from the umbilicus to the inferior border of the liver and joins the left branch of the portal vein. Small veins accompanying it connect the portal vein with veins around the umbilicus. These become prominent when the portal venous system is obstructed inside the liver.

The venous drainage from the liver is into the *right* and *left hepatic veins* which emerge from the back of the liver and at once enter the inferior vena cava very near its point of entry into the right atrium.

Lymphatic vessels terminate in small groups of glands around the porta hepatis. Efferent vessels drain into glands around the coeliac axis. Some superficial hepatic lymphatics pass through the diaphragm in the falciform ligament and finally reach the mediastinal glands. Another group accompanies the inferior vena cava into the thorax and ends in a few small glands around the intrathoracic portion of the inferior vena cava.

The *inferior vena cava* makes a deep groove to the right of the caudate lobe about 2 cm from the midline.

The *gallbladder* lies in a fossa extending from the inferior border of the liver to the right end of the porta hepatis.

The liver is completely covered with peritoneum, except in three places. It comes into direct contact with the diaphragm through the bare area which lies to the

Fig. 1.1 Anterior view of the liver.

Fig. 1.2 Posterior view of the liver.

Fig. 1.3 Inferior view of the liver.

right of the fossa for the inferior vena cava. The other areas without peritoneal covering are the fossae for the inferior vena cava and gallbladder.

The liver is kept in position by peritoneal ligaments and by the intra-abdominal pressure transmitted by the tone of the muscles of the abdominal wall.

Functional liver anatomy: sectors and segments

Based on the external appearances described earlier, the liver has a right and left lobe separated along the line of insertion of the falciform ligament. This separation, however, does not correlate with blood supply or biliary drainage. A *functional anatomy* is now recognized based upon vascular and biliary anatomy. The *Couinaud* classification [5] defines eight segments (segments I–IV in the left lobe, V–VIII in the right lobe), while the *Bismuth* classification [6] divides the liver into four sectors. These can be correlated with results seen with imaging techniques.

The main portal vein divides into right and left branches and each of these supplies two further subunits (variously called sectors). The sectors on the right side are anterior and posterior and, in the left lobe, medial
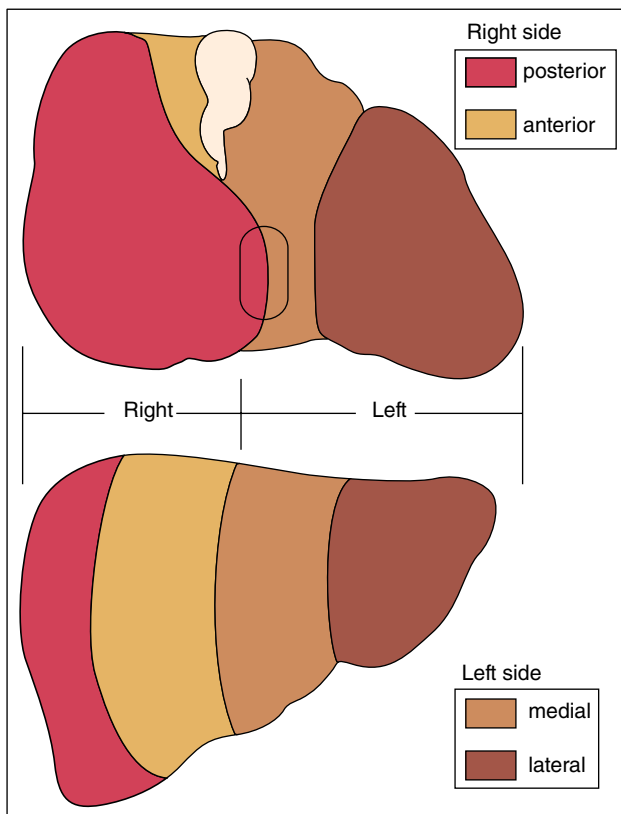
and lateral – giving a total of four sectors (Fig. 1.4). Using this definition, the right and left side of the liver are divided not along the line of the falciform ligament, but along a slightly oblique line to the right of this, drawn from the inferior vena cava above to the gallbladder bed below. The right and left side are independent with regard to portal and arterial blood supply, and bile drainage. Three planes separate the four sectors and contain the three major hepatic vein branches.

Closer analysis of these four hepatic sectors produces a further subdivision into segments (Fig. 1.5). The right anterior sector contains segments V and VIII; right posterior sector, VI and VII; left medial sector, IV; left lateral sector, II and III. There is no vascular anastomosis between the macroscopic vessels of the segments but communications exist at the sinusoidal level. Segment I, the equivalent of the caudate lobe, is separate from the other segments and does not derive blood directly from the major portal branches or drain by any of the three major hepatic veins.

This functional anatomical classification allows interpretation of radiological data and is of importance to the surgeon planning a liver resection. There are wide variations in portal and hepatic vessel anatomy which can be demonstrated by spiral computed tomography (CT) and magnetic resonance imaging (MRI) reconstruction [7].

Anatomical abnormalities of the liver

These are being increasingly diagnosed with more widespread use of CT and ultrasound scanning.

Accessory lobes. The livers of the pig, dog, and camel are divided into distinct and separate lobes by strands of connective tissue. Occasionally, the human liver may

Fig. 1.4 The sectors of the human liver.
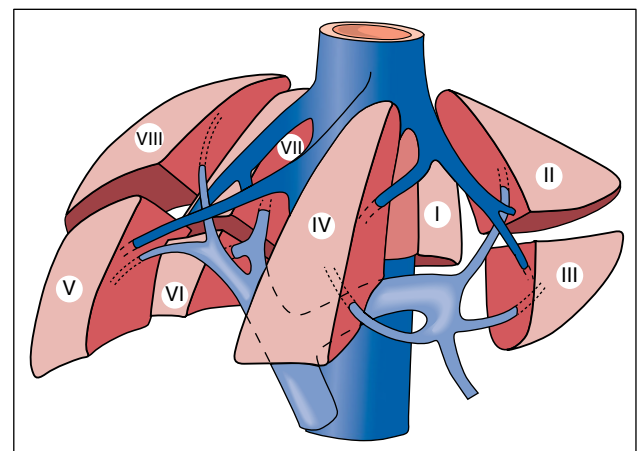
Fig. 1.5 Schematic representation of the functional anatomy of the liver. Three main hepatic veins (dark blue) divide the liver into four sectors, each of them receiving a portal pedicle; hepatic veins and portal veins are intertwined as the fingers of two hands [6].

show this reversion and up to 16 lobes have been reported. This abnormality is rare and without clinical significance. The lobes are small and usually on the undersurface of the liver so that they are not detected clinically but are noted incidentally at scanning, operation, or necropsy. Rarely, they are intrathoracic [8]. An accessory lobe may have its own mesentery containing hepatic artery, portal vein, bile duct, and hepatic vein. This may twist and demand surgical intervention.

Ectopic liver. Small nodules of normal liver derived from the embryologic hepatic bud may be found in less than 1% of laparoscopies and autopsies near the gallbladder, hepatic ligaments, gastrorenal ligament, omentum, retroperitorneum, and thorax. These may give rise to hepatocellular carcinoma [9,10].

Riedel's lobe. This is fairly common and is a downward tongue-like projection of the right lobe of the liver [11]. It is a simple anatomical variation; it is not a true accessory lobe. The condition is more frequent in women. It is detected as a mobile tumour on the right side of the abdomen which descends with the diaphragm on inspiration. It may come down as low as the right iliac region. It is easily mistaken for other tumours in this area, especially a visceroptotic right kidney. It does not cause symptoms and treatment is not required. Rarely, it is a site for metastasis or primary hepatocellular carcinoma. Scanning may be used to identify Riedel's lobe and other anatomical abnormalities.

Cough furrows on the liver. These are vertical grooves on the convexity of the right lobe. They are one to six in number and run anteroposteriorly, being deeper posteriorly. These represent diaphragmatic sulci and fissures produced by pressure exerted by diaphragmatic muscle on peripheral structurally weak liver parenchymal zones associated with watershed vascular distribution [12]. Chronic cough produces such pressure.

Corset liver. This is a horizontal fibrotic furrow or pedicle on the anterior surface of one or both lobes of the liver just below the costal margin [13]. The mechanism is unknown, but it affects elderly women who have worn corsets for many years. It presents as an abdominal mass in front of and below the liver and is isodense with the liver. It may be confused with a hepatic tumour.

Lobar atrophy. Interference with the portal supply or biliary drainage of a lobe may cause atrophy. There is usually hypertrophy of the opposite lobe. Left lobe atrophy found at post-mortem or during scanning is not uncommon and is probably related to reduced blood supply via the left branch of the portal vein. The lobe is decreased in size with thickening of the capsule, fibrosis, and prominent biliary and vascular markings. The vascular problem may date from the time of birth. Loss of left lobe parenchyma in this instance develops by the process of ischaemic extinction due to impaired flow from the affected large portal vein branch. Replacement

fibrosis ensues. This large vessel extinction process should be distinguished from cirrhosis in which the entire liver is affected by numerous intrahepatic and discrete extinction lesions, which affect small hepatic veins and portal vein branches during the course of inflammation and fibrosis. Hence, in cirrhosis the entire liver surface is diffusely converted to regenerative parenchymal nodules surrounded by fibrosis.

Obstruction to the right or left hepatic bile duct by benign stricture or cholangiocarcinoma is now the most common cause of lobar atrophy [14]. The alkaline phosphatase is usually elevated. The bile duct may not be dilated within the atrophied lobe. Relief of obstruction may reverse the changes if cirrhosis has not developed. Distinction between a biliary and portal venous aetiology may be made using technetium-labelled iminodiacetic acid (IDA) and colloid scintiscans. A small lobe with normal uptake of IDA and colloid is compatible with a portal aetiology. Reduced or absent uptake of both isotopes favours biliary disease.

Agenesis of the right lobe [15]. This rare lesion may be an incidental finding associated, probably coincidentally, with biliary tract disease and also with other congenital abnormalities. It can cause presinusoidal portal hypertension. The other liver segments undergo compensatory hypertrophy. It must be distinguished from lobar atrophy due to cirrhosis or hilar cholangiocarcinoma.

Situs inversus (SI). In the exceedingly rare *SI totalis* or *abdominalis* the liver is located in the left hypochondrium and may be associated with other anomalies including biliary atresia, polysplenia syndrome, aberrant hepatic artery anatomy, and absent portal vein. Hepatic surgery (partial hepatectomy, liver transplantation) is feasible, but complex. Other conditions associated with displacement of the liver from its location in the right upper quadrant include *congenital diaphragmatic hernias, diaphragmatic eventration,* and *omphalocoele.*

Anatomical abnormalities of the gallbladder and biliary tract are discussed in Chapter 14.

Anatomy of the biliary tract (Fig. 1.6)

The *right* and *left hepatic ducts* emerge from the liver and unite in the porta hepatis to form the *common hepatic duct.* This is soon joined by the *cystic duct* from the gallbladder to form the common bile duct.

The *common bile duct* runs between the layers of the lesser omentum, lying anterior to the portal vein and to the right of the hepatic artery. Passing behind the first part of the duodenum in a groove on the back of the head of the pancreas, it enters the second part of the duodenum. The duct runs obliquely through the posteromedial wall, usually joining the main pancreatic duct to form the *ampulla of Vater* (*c*. 1720). The ampulla makes the
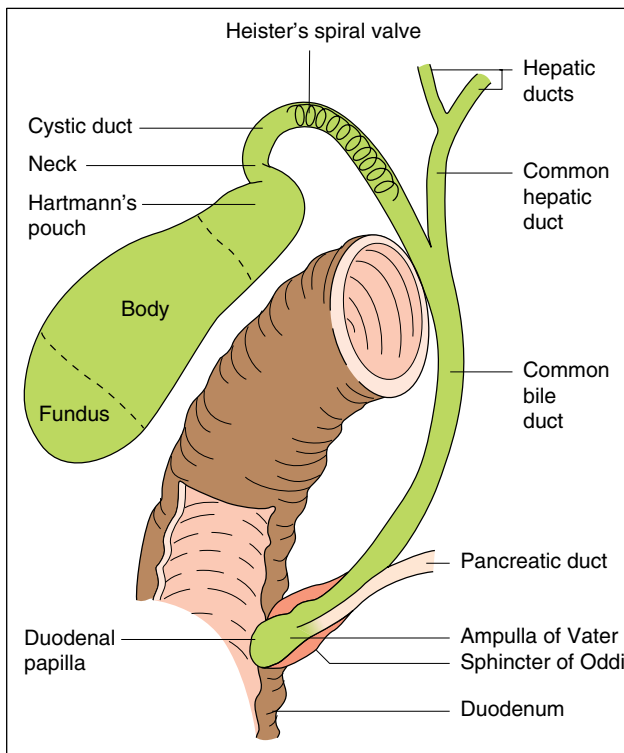
Fig. 1.6 Gallbladder and biliary tract.

mucous membrane bulge inwards to form an eminence, the *duodenal papilla*. In about 10–15% of subjects the bile and pancreatic ducts open separately into the duodenum.

The dimensions of the common bile duct depend on the technique used. At operation it is about 0.5–1.5 cm in diameter. Using ultrasound the values are less, the common bile duct being 2–7 mm, with values greater than 7 mm being regarded as abnormal. Using endoscopic cholangiography, the duct diameter is usually less than 11 mm, although after cholecystectomy it may be more in the absence of obstruction.

The duodenal portion of the common bile duct is surrounded by a thickening of both longitudinal and circular muscle fibres derived from the intestine. This is called the *sphincter of Oddi* (*c.* 1887).

The *gallbladder* is a pear-shaped bag 9 cm long with a capacity of about 50 mL. It always lies above the transverse colon, and is usually next to the duodenal cap overlying, but well anterior to, the right renal shadow. The fundus is the wider end and is directed anteriorly; this is the part palpated when the abdomen is examined. The body extends into a narrow neck which continues into the cystic duct. The *valves of Heister* are spiral folds of mucous membrane in the wall of the cystic duct and neck of the gallbladder. *Hartmann's pouch* is a sacculation at the neck of the gallbladder; this is a common site for a gallstone to lodge.

The mucosa is in delicate, closely woven folds; instead of glands there are indentations of mucosa which usually lie superficial to the muscle layer. Increased intraluminal pressure in chronic cholecystitis results in formation of branched, diverticula-like invaginations of the mucosa which reach into the muscular layer, termed *Rokitansky–Aschoff sinuses*. There is no submucosa or muscularis mucosae. The gallbladder wall consists of a loose connective tissue lamina propria and muscular layer containing circular, longitudinal, and oblique muscle bundles without definite layers, the muscle being particularly well developed in the neck and fundus. The outer layers are the subserosa and serosa. The distensible normal gallbladder fills with bile and bile acids secreted by the liver, concentrates the bile through absorption of water and electrolytes and with meals contracts under the influence of cholecystokinin (acting through preganglionic cholinergic nerves) to empty bile into the duodenum.

Blood supply. The gallbladder receives blood from the *cystic artery*. This branch of the hepatic artery is large, tortuous, and variable in its anatomical relationships. Smaller blood vessels enter from the liver through the gallbladder fossa. The venous drainage is into the *cystic vein* and thence into the portal venous system. Attention to the vascular-biliary anatomy in the reference area known as *Calot's triangle* (bordered by the cystic duct, common hepatic duct, and lower edge of the liver) reduces the risk of vascular injuries and potential biliary strictures. Most bile duct injuries occur at cholecystectomy (incidence of <1.3% for either open or laparoscopic cholecystectomy). After liver transplantation 10–33% of patients may develop biliary complications, of which biliary stricture is the most important.

The arterial blood supply to the supraduodenal bile duct is generally by two main (axial) vessels which run beside the bile duct. These are supplied predominantly by the retroduodenal artery from below, and the right hepatic artery from above, although many other vessels contribute. This pattern of arterial supply would explain why vascular damage results in bile duct stricturing [16].

Lymphatics. There are many lymphatic vessels in the submucous and subperitoneal layers. These drain through the cystic gland at the neck of the gallbladder to glands along the common bile duct, where they anastomose with lymphatics from the head of the pancreas.

Nerve supply. The gallbladder and bile ducts are liberally supplied with nerves, from both the parasympathetic and the sympathetic system.

Surface marking (Fig. 1.7, Fig. 1.8)

Liver. The upper border of the right lobe is on a level with the 5th rib at a point 2 cm medial to the right midclavicular line (1 cm below the right nipple). The upper border

of the left lobe corresponds to the upper border of the 6th rib at a point in the left midclavicular line (2 cm below the left nipple). Here only the diaphragm separates the liver from the apex of the heart.

The lower border passes obliquely upwards from the 9th right to the 8th left costal cartilage. In the right nipple line it lies between a point just under to 2 cm below the costal margin. It crosses the midline about midway between the base of the xiphoid and the umbilicus and the left lobe extends only 5 cm to the left of the sternum.

Gallbladder. Usually the fundus lies at the outer border of the right rectus abdominis muscle at its junction with the right costal margin (9th costal cartilage) (Fig. 1.8). In an obese subject it may be difficult to identify the outer border of the rectus sheath and the gallbladder may then be located by the Grey–Turner method. A line is drawn from the left anterior superior iliac spine through the umbilicus; its intersection with
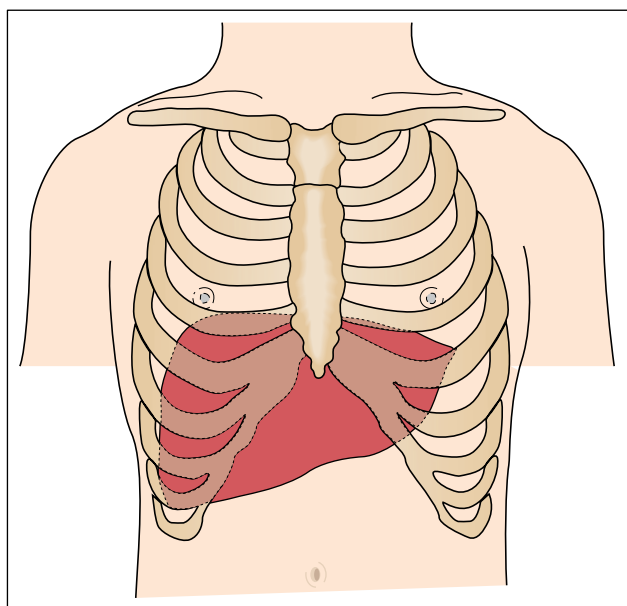
the right costal margin indicates the position of the gallbladder. These guidelines depend upon the individual's build. The fundus may occasionally be found below the iliac crest.

Methods of examination

Liver. The lower edge should be determined by palpation just lateral to the right rectus muscle. This avoids mistaking the upper intersection of the rectus sheath for the liver edge.

The liver edge moves 1–3 cm downwards with deep inspiration. It is usually palpable in normal subjects inspiring deeply. The edge may be tender, regular or irregular, firm or soft, thickened or sharp. The lower edge may be displaced downwards by a low diaphragm, for instance in emphysema. Movements may be particularly great in athletes or singers. Some patients with practice become very efficient at 'pushing down' the liver. The normal spleen can become palpable in similar fashion. Common causes of a liver palpable below the umbilicus are malignant deposits, polycystic or Hodgkin disease, amyloidosis, congestive cardiac failure, and gross fatty change. Rapid change in liver size may occur when congestive cardiac failure is corrected, cholestatic jaundice relieved, or when severe diabetes is controlled. The surface can be palpated in the epigastrium and any irregularity or tenderness noted. An enlarged caudate lobe, as in the Budd–Chiari syndrome or with some cases of cirrhosis, may be palpated as an epigastric mass.

Pulsation of the liver, usually associated with tricuspid valvular incompetence, is felt by manual palpation with one hand behind the right lower ribs posteriorly and the other anteriorly on the abdominal wall.

The upper edge is determined by fairly heavy percussion passing downwards from the nipple line. The lower edge is recognized by very light percussion passing upwards from the umbilicus towards the costal margin. Percussion is a

Fig. 1.7 The surface marking of the liver.

Fig. 1.8 Surface markings of the gallbladder. Method I: the gallbladder is found where the outer border of the right rectus abdominis muscle intersects the 9th costal cartilage. Method II: a line drawn from the left anterior superior iliac spine through the umbilicus intersects the costal margin at the site of the gallbladder.
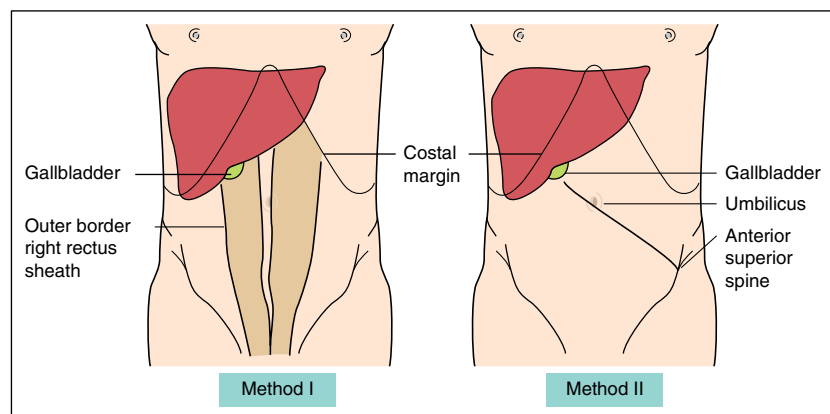
valuable method of determining liver size and is the only clinical method of determining a small liver.

The anterior liver span is obtained by measuring the vertical distance between the uppermost and lowermost points of hepatic dullness by percussion in the right midclavicular line. This is usually 12–15 cm. Direct percussion is as accurate as ultrasound in estimating liver span [17].

Friction may be palpable and audible, usually due to recent biopsy, tumour, or perihepatitis. The venous hum of portal hypertension is audible between the umbilicus and the xiphisternum. An arterial murmur over the liver may indicate a primary liver cancer or acute alcoholic hepatitis.

Gallbladder. The gallbladder is palpable only when it is distended. It is felt as a pear-shaped cystic mass usually about 7 cm long. In a thin person, the swelling can sometimes be seen through the anterior abdominal wall. It moves downwards on inspiration and is mobile laterally but not downwards. The swelling is dull to percussion and directly impinges on the parietal peritoneum, so that the colon is rarely in front of it. Gallbladder dullness is continuous with that of the liver.

Abdominal tenderness should be noted. Inflammation of the gallbladder causes a positive *Murphy's sign*. This is the inability to take a deep breath when the examining fingers are hooked up below the liver edge. The inflamed gallbladder is then driven against the fingers and the pain causes the patient to catch their breath.

The enlarged gallbladder must be distinguished from a *visceroptotic right kidney.* This, however, is more mobile, can be displaced towards the pelvis and has the resonant colon anteriorly. A *regenerative* or *malignant nodule* feels much firmer.

Imaging. A plain film of the abdomen, including the diaphragms, may be used to assess liver size and in particular to decide whether a palpable liver is due to actual enlargement or to downward displacement. On moderate inspiration the normal level of the diaphragm, on the right side, is opposite the 11th rib posteriorly and the 6th rib anteriorly.

Ultrasound, CT, or MRI can be used to study liver size, shape, and content.

Microanatomy of the liver

For over a century, many models of liver substructure have been proposed [18]. The most popular of these is the *lobule* introduced by Kiernan in 1833 as the basic architectural unit, based on pig dissections [19]. He described circumscribed, hexagonal lobules consisting of a central tributary of the hepatic vein (central vein) and at the periphery a portal tract containing the bile duct, portal vein radicle, and hepatic artery branch. Cords (plates) of liver cells and blood-containing sinusoids extend between these two systems. The lobule has foundations in pig, camel, raccoon, and polar bear livers, in which such hexagonal units are surrounded by interlobular connective tissue septa [20]. Such septa have no counterparts in human liver.

Stereoscopic reconstructions and scanning electron microscopy have shown the human liver as cords of liver cells radiating from a central vein, and interlaced in orderly fashion by sinusoids (Figs 1.9, 1.10). The terminal branches of the portal vein discharge their blood into the sinusoids and the direction of flow is determined by the higher pressure in the portal vein than in the central vein (or terminal hepatic venule) – see later.

The *portal tracts* are small connective tissue islands containing triads composed of the portal vein radicle, the hepatic arteriole, and bile duct (Fig. 1.11). Portal tracts are surrounded by a limiting plate of liver cells. Histological sections of normal liver show portal tracts containing dyads as frequently as triads, with the portal vein being the most frequently absent element. Within each linear centimetre of liver tissue obtained at biopsy there are usually two interlobular bile ducts, two hepatic arteries and one portal vein per portal tract, with six full portal triads [21].

The liver has to be divided *functionally*. Traditionally, the unit is based on a central hepatic vein and its surrounding liver cells. However, Rappaport [22] envisages a series of functional *acini,* each centred on the portal tract with its terminal branch of portal vein, hepatic artery, and bile duct (zone 1) (Fig. 1.12, Fig. 1.13). These interdigitate, mainly perpendicularly, with terminal hepatic veins of adjacent acini. The circulatory peripheries of acini (adjacent to terminal hepatic veins) (zone 3) suffer most from injury, whether viral, toxic, or anoxic. Bridging necrosis may extend from the periphery (acinar zone 1) to zone 3. The regions closer to the axis formed by afferent vessels and bile ducts survive longer and may later form the core from which regeneration will proceed. The contribution of each acinar zone to liver cell regeneration depends on the acinar location of damage [22].

The liver cells (*hepatocytes*) comprise about 60% of the liver. They are polygonal and approximately 30 μm in diameter. The nucleus is single or, less often, multiple and divides by mitosis. The lifespan of liver cells is about 150 days in experimental animals. The hepatocyte has three surfaces: one facing the sinusoid and space of Disse, the second facing the canaliculus, and the third facing neighbouring hepatocytes (Fig. 1.14). There is no basement membrane.

The sinusoids are lined by endothelial cells with small pores (fenestrae) for macromolecule diffusion from
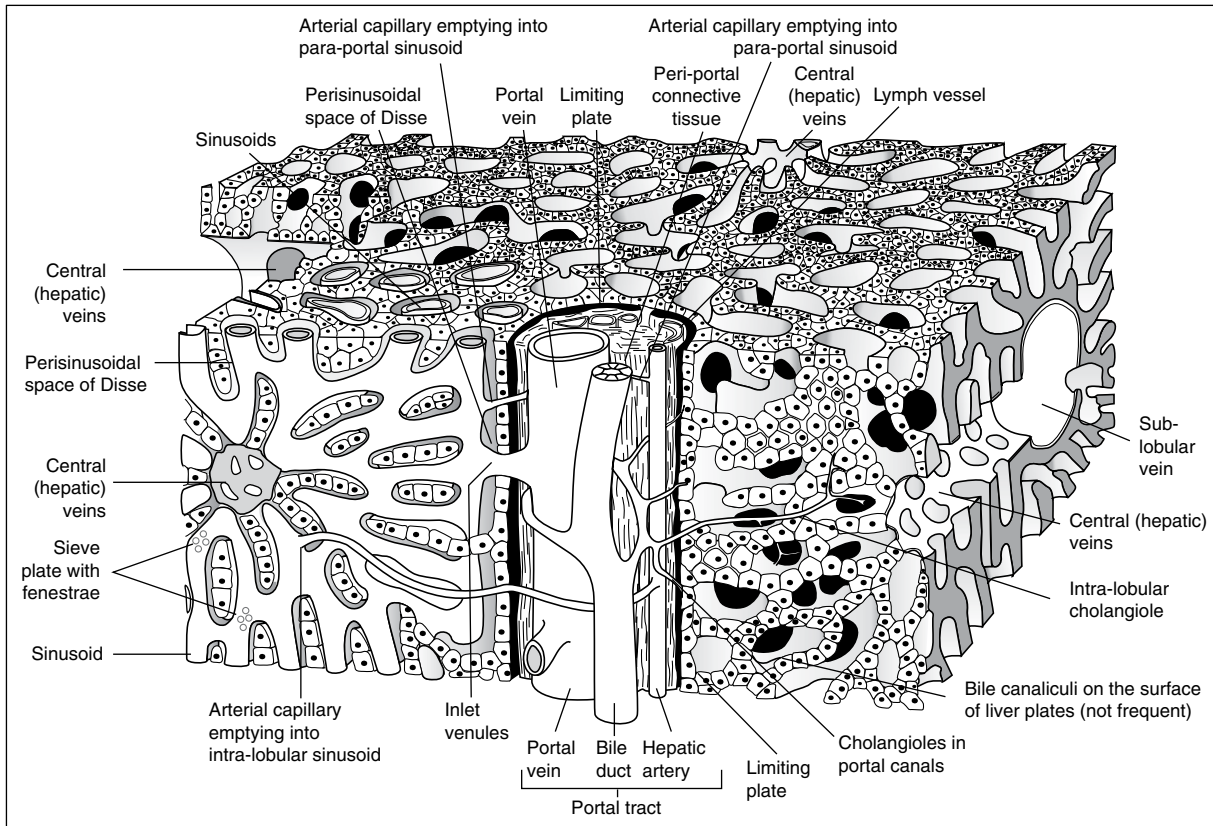
Fig. 1.9 The structure of the normal human liver.
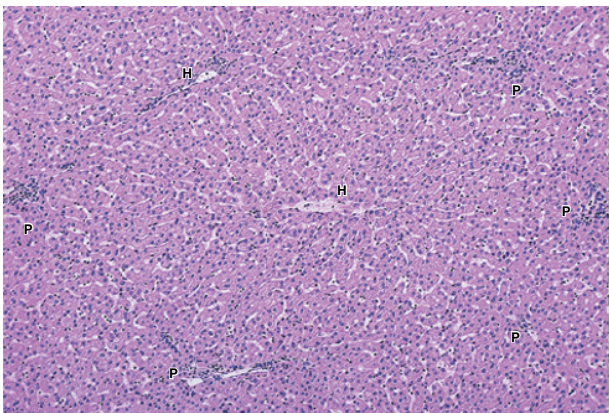
Fig. 1.10 Normal hepatic histology. H, terminal hepatic vein; P, portal tract. (H & E, ×60.)
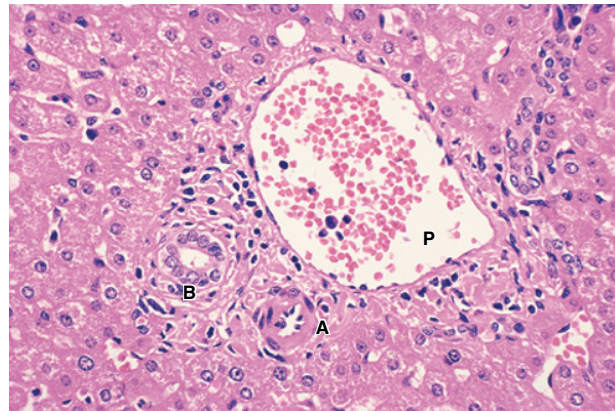
Fig. 1.11 Normal portal tract. A, hepatic artery; B, bile duct; P, portal vein. (H & E.)

blood to hepatocytes. On the vascular side of the sinusoids are the phagocytic cells of the reticulo-endothelial system (Kupffer cells) and pit cells (NK or natural killer cells) which are cytotoxic lymphoid cells involved in surveillance for tumour cells and viral infections [23,24].

There are approximately 202×10^3 cells in each milligram of normal human liver, of which 171×10^3 are parenchymal and 31×10^3 littoral (sinusoidal, including Kupffer cells).

The *space of Disse* between hepatocytes and sinusoidal endothelial cells contains a few collagen fibrils and the hepatic stellate cells, which have also been called fat-storing cells, Ito cells, and lipocytes. These cells store vitamin A and when activated in disease become collagen-synthesizing myofibroblasts. The *hepatic lymphatics* are found in the periportal connective tissue and are lined throughout by endothelium. Tissue fluid seeps through the endothelium into the lymph vessels.
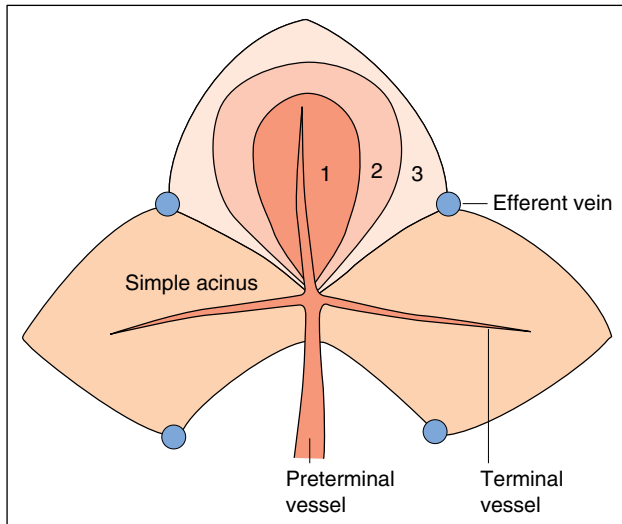
Fig. 1.12 The complex acinus according to Rappaport. Zone 1 is adjacent to the entry (portal venous) system. Zone 3 is adjacent to the exit (hepatic venous) system.
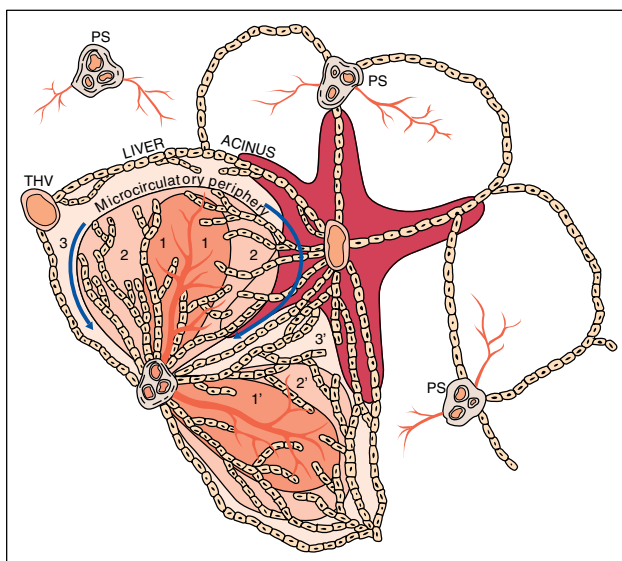
Fig. 1.13 Blood supply of the simple liver acinus, zonal arrangements of cells and the microcirculatory periphery. The acinus occupies adjacent sectors of the neighbouring hexagonal fields. Zones 1, 2, and 3, respectively, represent areas supplied with blood of first, second, and third quality with regard to oxygen and nutrient content. These zones centre on the terminal afferent vascular branches, bile ductules, lymph vessels, and nerves (PS) and extend into the triangular portal field from which these branches crop out. Zone 3 is the microcirculatory periphery of the acinus since its cells are as remote from their own afferent vessels as from those of adjacent acini. The *perivenular* area is formed by the most peripheral portions of zone 3 of several adjacent acini. In injury progressing along this zone, the damaged area assumes the shape of a starfish (darker tint around a terminal hepatic venule [THV] in the centre). 1–3, microcirculatory zones; 1′–3′, zones of neighbouring acinus [22].

The branch of the *hepatic arteriole* forms a plexus around the bile ducts and supplies the structures in the portal tracts. It empties into the sinusoidal network at different levels. There are no direct hepatic arteriolar–portal venous anastomoses.

The excretory system of the liver begins with the *bile canaliculi* (Fig. 1.14, Fig. 1.15). These are formed by modifications of the contact surfaces of liver cells and are covered by microvilli. The plasma membrane is reinforced by microfilaments forming a supportive cytoskeleton. The canalicular surface is sealed from the rest of the intercellular surface by junctional complexes including tight junctions, gap junctions, and desmosomes. The intralobular canalicular network drains into the canals of Hering lined by low cuboidal epithelium which connect via short bile ductules to the larger terminal bile ducts within the portal tracts. Bile ducts are classified into small (less than 100 μm in diameter), medium (about 100 μm), and large (more than 100 μm) calibre types.

Hepatic ultrastructure (electron microscopy) and organelle functions

Hepatocytes (Fig. 1.14, Fig. 1.15, Fig. 1.16, Fig. 1.17)

The liver cell margin is straight except for a few anchoring pegs (desmosomes). From it, equally sized and spaced microvilli project into the lumen of the bile canaliculi. Along the sinusoidal border, irregularly sized and spaced microvilli project into the perisinusoidal tissue space. The microvillous structure indicates active secretion or absorption, mainly of fluid.

The *nucleus* has a double contour with pores allowing interchange with the surrounding cytoplasm. Human liver after puberty contains tetraploid nuclei and, at about age 20, in addition, octoploid nuclei are found. Increased polyploidy has been regarded as precancerous. In the chromatin network one or more nucleoli are embedded.

The *mitochondria* also have a double membrane, the inner being invaginated to form grooves or cristae. An enormous number of energy-providing processes take place within them, particularly those involving oxidative phosphorylation. They contain many enzymes, particularly those of the citric acid cycle and those involved in β-oxidation of fatty acids. They can transform energy so released into adenosine diphosphate (ADP). Haem synthesis occurs here.

The *rough endoplasmic reticulum* (RER) is seen as lamellar structures lined by ribosomes. These are responsible for basophilia under light microscopy. They synthesize specific proteins, particularly albumin, those
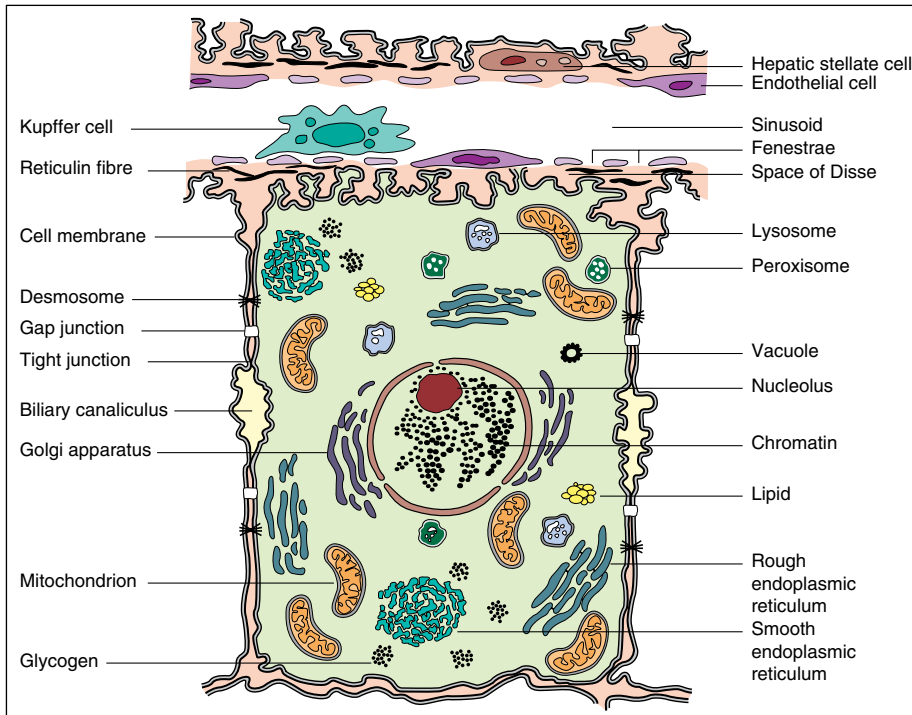
Fig. 1.14 The organelles of the liver cell.
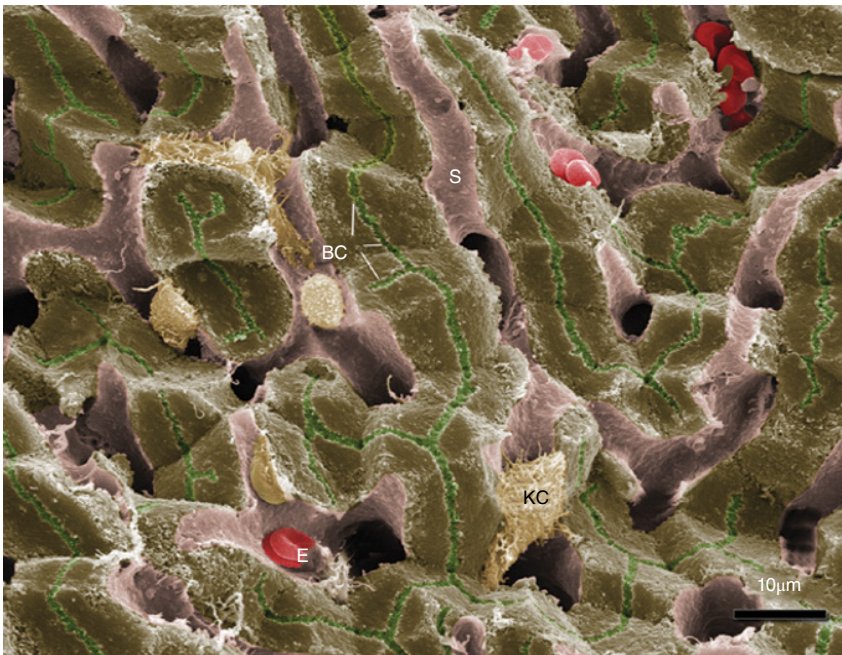
Fig. 1.15 Colourized scanning electron micrograph of liver showing hepatocytes in green, sinusoids (S) in light pink, erythrocytes (E), Kupffer cells (K), and bile canaliculi (BC). Courtesy of Ms Jackie Lewin, UCL Medical School, London.

used in blood coagulation and enzymes. They may adopt a helix arrangement, as polysomes, for coordination of this function. Glucose-6-phosphatase is synthesized. Triglycerides are synthesized from free fatty acids and complexed with protein to be secreted by exocytosis as lipoprotein. The RER may participate in glycogenesis.

The *smooth endoplasmic reticulum* (SER) forms tubules and vesicles. It contains the microsomes. It is the site of bilirubin conjugation and the detoxification of many drugs and other foreign compounds (P450 systems). Steroids are synthesized, including cholesterol and the primary bile acids, which are conjugated with the
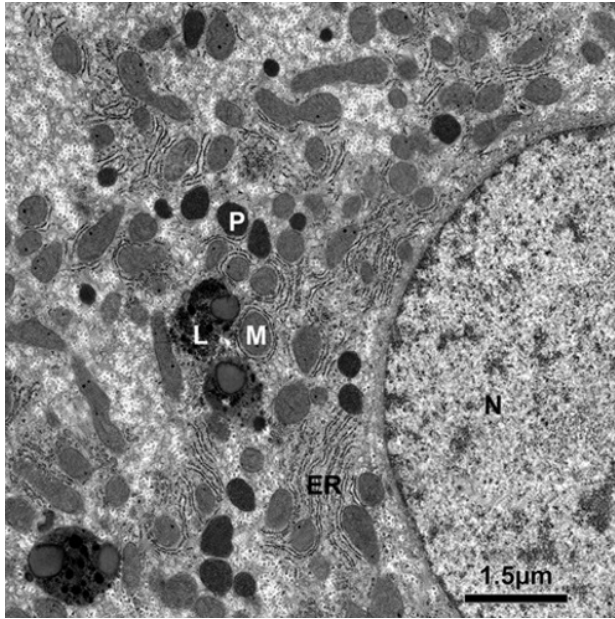
Fig. 1.16 Electron microscopic appearances of part of a normal human liver cell. N, nucleus; M, mitochondrion; P, peroxisome; L, lysosome; ER, rough endoplasmic reticulum. Courtesy of Ms Jackie Lewin, UCL Medical School, London.
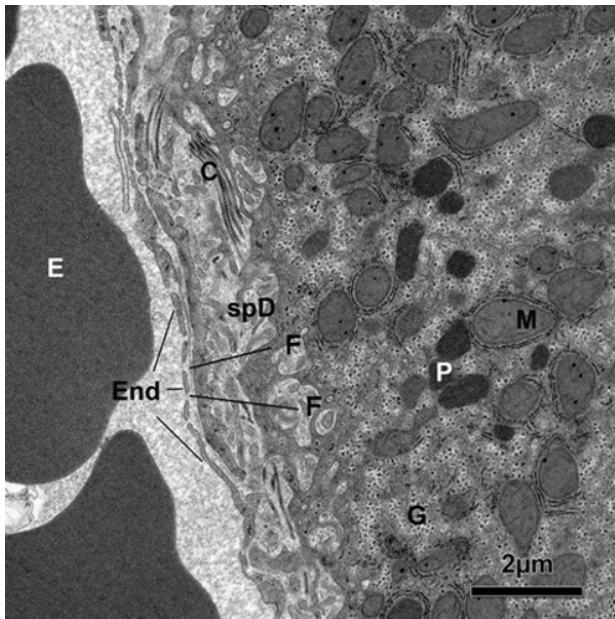
Fig. 1.17 Transmission electron micrograph showing an hepatocyte (right) with its microvillus membrane surface facing onto the space of Disse (spD) and the overlying endothelium (End). The endothelium has fenestrations (F) and there are a few collagen bundles (C) in the space of Disse. Erythrocytes (E) are present within the sinusoidal lumen. M, mitochondrion; P, peroxisome; G, glycogen granules. Courtesy of Ms Jackie Lewin, UCL Medical School, London.

amino acids glycine and taurine. The SER is increased by enzyme inducers such as phenobarbital.

Peroxisomes are versatile organelles, which have complex catabolic and biosynthetic roles, and are distributed near the SER and glycogen granules. Peroxisomal enzymes include simple oxidases, β-oxidation cycles, the glyoxalate cycle, ether lipid synthesis, and cholesterol and dolichol biosynthesis. Several disorders of peroxisomal function are recognized of which Zellweger syndrome is one [25]. Endotoxin severely damages peroxisomes [26].

The *lysosomes* are membrane-bound, electron-dense bodies adjacent to the bile canaliculi. They contain many hydrolytic enzymes which, if released, could destroy the cell. They are the site of deposition of ferritin, lipofuscin, bile pigment, copper, and senescent organelles.

The *Golgi apparatus* consists of a system of particles and vesicles, again lying near the canaliculus. It may be regarded as a 'packaging' site before excretion into the bile. This entire group of lysosomes, microbodies, and Golgi apparatus is a means of sequestering any material that is ingested and has to be excreted, secreted, or stored for metabolic processes in the cytoplasm. The Golgi apparatus, lysosomes, and canaliculi are concerned in cholestasis (Chapter 13).

The intervening cytoplasm contains granules of glycogen, lipid, and ferritin.

The *cytoskeleton* supporting the hepatocyte consists of microtubules, microfilaments, and intermediate filaments [27]. Microtubules contain tubulin and control subcellular mobility, vesicle movement, and plasma protein secretion. Microfilaments are made up of actin, are contractile and are important for the integrity and motility of the canaliculus and for bile flow. Intermediate filaments are elongated branched filaments comprising cytokeratins [1]. They extend from the plasma membrane to the perinuclear area and are fundamental for the stability and spatial organization of the hepatocyte. They become disrupted or lost with hepatocellular injury by alcohol, lipid peroxidation by-products, and ischaemia [28].

Sinusoidal cells

The sinusoidal cells (endothelial cells, Kupffer cells, hepatic stellate cells, and pit cells) form a functional and histological unit together with the sinusoidal aspect of the hepatocyte [29]. These cells interact via cytokines and other signalling mechanisms [30,31]. The close structural relationship of sinusoidal cells to hepatic cords is evident on transmission (Fig. 1.17) and scanning electron microscopy (Fig. 1.15).

Endothelial cells line the sinusoids and have fenestrae, which provide a graded barrier between the sinusoid and space of Disse (Fig. 1.18). The Kupffer cells anchor on the endothelium by their cytoplasmic projections.
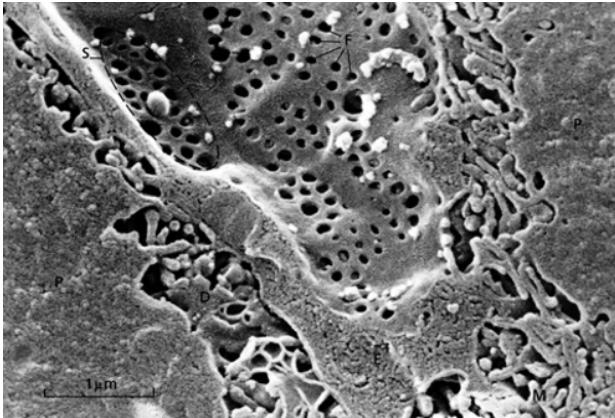
Fig. 1.18 Scanning electron micrograph of sinusoid showing fenestrae (F) grouped into sieve plates (S). D, space of Disse; E, endothelial cell; M, microvilli; P, parenchymal cell. Courtesy of Professor E. Wisse.
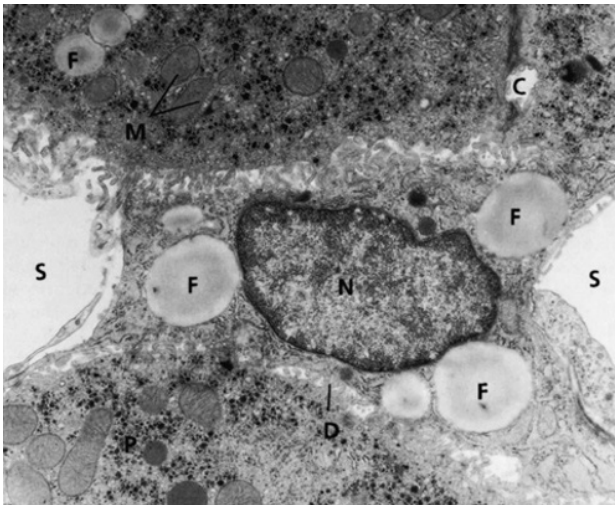
Fig. 1.19 Transmission electron micrograph of an hepatic stellate cell. Note the characteristic fat droplets (F). C, bile canaliculus; D, space of Disse; M, mitochondria; N, nucleus; P, parenchymal cell; S, lumen of sinusoid. (×12 000) Courtesy of Professor E. Wisse.

The hepatic stellate cells lie in the space of Disse between the hepatocytes and the endothelial cells (Fig. 1.19). *Disse's space* contains tissue fluid which flows outwards into lymphatics in the portal zones. When sinusoidal pressure rises, lymph production in Disse's space increases and this plays a part in ascites formation where there is hepatic venous outflow obstruction.

Endothelial cells. These cells form a continuous lining to the sinusoids. They differ from endothelial cells elsewhere in not having a regular basement membrane. The endothelial cells act as a sieve between the sinusoid and space of Disse, have specific and non-specific endocytotic activity and have a variety of receptors. Their capacity to act as a sieve is due to fenestrae, around 0.15 μm in

diameter (Fig. 1.18). These make up 6–8% of the total endothelial cell surface, and there are more in the centrilobular zone of the sinusoid than the periportal area. Extracellular matrix affects their function.

Fenestrae are clustered into sieve plates, and act as biofilters and transport pores between sinusoidal blood and the plasma within the space of Disse. They have a dynamic cytoskeleton [32]. This maintains and regulates their size, which can be changed by many influences including alcohol, nicotine, serotonin, endotoxin, and partial hepatectomy. The fenestrae filter macromolecules of differing size. Particles greater than 0.2 μm in diameter, which include large triglyceride-rich parent chylomicrons, will not pass. Smaller triglyceride-depleted, cholesterol-rich, and retinol-rich remnants can enter the space of Disse [33]. In this way the fenestrae have an important role in chylomicron and lipoprotein metabolism. Open fenestrae, which are located in the thin cytoplasmic periphery of the endothelial cells while close to the endothelial nuclei fenestrae, are multifolded and labyrinth-like [34].

Endothelial cells have a high capacity for endocytosis (accounting for 45% of all pinocytotic vesicles in the liver) and are active in clearing macromolecules and small particles from the circulation [35]. Coated and uncoated membrane-bound vesicles on endothelium are present near their nuclei or on non-fenestrated portions of their cytoplasm [36]; these are involved in various endocytic functions. There is receptor-mediated endocytosis for several molecules including transferrin, caeruloplasmin, modified high-density lipoprotein (HDL) and low-density lipoprotein (LDL), hepatic lipase and very low-density lipoprotein (VLDL). Hyaluronan (a major polysaccharide from connective tissue) is taken up and this provides a method for assessing hepatic endothelial cell capacity. Endothelial cells can also clear small particles (<0.1 μm) from the circulation, as well as denatured collagen. Scanning electron microscopy has shown a striking reduction in the number of fenestrae, particularly in zone 3 in alcoholic patients, with formation of a basal lamina, which is also termed capillarization of the sinusoid [37].

Kupffer cells. These are highly mobile macrophages attached to the endothelial lining of the sinusoid, in greater numbers in the periportal areas [38]. They have microvilli and intracytoplasmic-coated vesicles and dense bodies which make up the lysosomal apparatus. They proliferate locally but under certain circumstances macrophages can immigrate from an extrahepatic site. They are responsible for removing old and damaged blood cells or cellular debris, also bacteria, viruses, parasites, and tumour cells. They do this by endocytosis (phagocytosis, pinocytosis), including absorptive (receptor-mediated) and fluid phase (non-receptor-mediated)